# Sexuality and preventive aspects of female reproduction

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# 1. THE OVARIAN CYCLE

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## PHASES OF THE OVARIAN CYCLE

**Prefollicular phase: maturation.** (passage from primordial follicle to preantral follicle). The substances and mechanisms that regulate the prefollicular phase and its duration in humans is unknown; we only know that it is independent of gonadotrophins. It appears that its regulation is determined by local factors that can not be stopped. It occurs invariably both during ovulatory cycles and in naturally anovulatory times, such as childhood, pregnancy, or when taking hormonal contraceptives. Therefore, parity, the age of menarche, or use of hormonal preparations have no influence on the age of onset of menopause in women.

**Growth** (passage from very small preantral follicle to preantral follicle initiating formation of the antrum). Once the follicles reach the preantral stage, follicle-stimulating hormone (FSH) acts on them to promote cell proliferation and differentiation so that the oocyte increases in size and surrounds itself with a membrane (the zona pellucida). While this process occurs, the cells of the granulosa undergo proliferation in multiple layers, and the thecal layer is organized from the surrounding stroma. In these follicles, estrogen is primarily synthesized. While we do not know what triggers growth, it is known to occur approximately 85 days before ovulation. The androgens produced in the thecal layer mark follicular development:

- At low concentrations, they will induce the expression of the P450 aromatase enzyme and will serve as a substrate for the synthesis of estrogens in granulosa cell (GC) aromatization.
- At high concentrations, overloading the aromatase capacity, the androgens are metabolized into more powerful substances that have the capacity to trigger apoptosis of the GCs.

**Recruitment or rescue** (passage from preantral follicle to antral follicle). The authors prefer the term "rescue" to the originally used term "recruitment" because of what actually occurs in the follicles that initiates maturation and growth is a rescue of the atresia for which they were predestined.

## FOLLICULAR PHASE

**Early follicular phase and selection of the dominant follicle.** Following the usual pattern, only a few antral follicles will be rescued from atresia and will reach the seventh day of the cycle. That is, of the cohort of preantral follicles rescued, only 5% will be selected. This selection (and subsequent dominance) will only be achieved by medium antral follicles that respond to the increase in FSH that occurs at the beginning of the menstrual cycle. In this stage, two fundamental phenomena will occur that will mark this selection: the presence of luteinizing hormone (LH) in the GC and the differentiation of a group of these that do not express these LH and that surround the oocyte (the ovarian cluster). The function of GC without LH is directed by the oocyte.

**The preovulatory follicle.** In the dominant follicle that prepares for ovulation, most GCs express luteinizing hormone receptors (LHRs) in their membranes. However, a specialized group of these, the ovarian cluster, maintain their membranes without these receptors. We now know that the oocyte itself directs the

specialization of its inner membrane, which continues to respond only to the FSH, the protection of which allows it to continue its meiosis.

During the follicular phase, estrogen levels and ovarian peptides (especially inhibin) grow, and the secretion of gonadotropin-releasing hormone (GnRH) and the two gonadotropins (negative feedback mechanism) is inhibited. However, an increase of estrogen at the end of the follicular phase is triggered by a positive feedback mechanism on the hypothalamic nuclei, creating a peak in the secretion of LH. Ovulation cannot occur without this peak of LH. High doses of estrogen are needed for a long time so that the usual inhibition of estrogen on the synthesis of LH turns to stimulation.

The mid-cycle increase in LH is responsible for atresia of any selected nondominant follicle and prepares the dominant follicle's GC for luteinization, that is, a change in their metabolism that makes them stop growing and synthesize more progesterone. This mechanism by which the growth of the GC is retarded and the energy effort focused on the production of progesterone is also unique to primates and does not occur in other species.

Comparatively, progesterone facilitates the positive feedback of estrogens on LH as long as it is maintained in low doses, as it achieves the opposite at higher doses. tThis is the natural ovarian instrument for preventing follicular development if pregnancy occurs and also the mechanism of action of hormonal contraceptives in any form. In addition, the low dose of progesterone released at this time is responsible for the peak of FSH that occurs in the middle of the cycle. GCs disappear due to apoptosis in all other follicles that have not reached dominance, while CTs are incorporated into the ovarian stroma and continue responding to LH with the synthesis of more androgens. In addition to contributing to the atresia of the follicles, this mesocyclic androgenic peak is responsible for the increase in libido experienced by some women.

**Ovulation.** The peak in LH precedes ovulation by 10 to 12 hours and is maintained for approximately 48 hours. Its presence is essential for ovulation and postovulatory hormonal production. The sequence is as follows:

1. luteinization of the GC
2. the peak of FSH in the middle of the cycle is less marked than that of LH and its purpose, apart from inducing LHR in the GC, is also to rescue the follicles that are going to develop in the following cycles
3. in the oocyte, meiosis resumes, reaching metaphase II
4. in response to intrafollicular hormonal changes, an increase in the synthesis of prostaglandins occurs. The physical expulsion of the oocyte depends on a vertiginous increase in the synthesis of prostaglandins in the follicle before ovulation
5. finally, an acute distention of the antrum is produced, and an avascular zone is created on its surface, where the follicle is broken and the ovum is expelled.

**Luteal phase.** Estradiol and progesterone are produced during the 14 days of this phase depending on the quantities of LH in the luteal phase. Lacking a growing source of GC from satisfactory implantation, the corpus luteum ages rapidly. Its vascularization and lipid content disappear, and its healing occurs. The function of this follicular luteinization is to produce progesterone, the hormone responsible for the maintenance of pregnancy. Similarly, progesterone modifies the physical, rheological, and biochemical characteristics of the cervical mucus, making it hostile to penetration via sperm. In addition, by increasing blood levels, it suppresses GnRH secretion through a powerful negative feedback effect, both at the hypothalamic level by decreasing GnRH secretion, and at pituitary level by blocking its action on gonadotrope cells. Progesterone has a thermogenic effect.

**Luteo-follicular transition.** If pregnancy does not occur, the first manifestation of luteolysis is the cessation of progesterone production. Consequently, biochemical changes will be induced in the endometrium along with the microarchitecture responsible for its complete desquamation. The degeneration of the corpus luteum also decreases the production of estrogen and inhibin, which results in the following neuroendocrine processes that will lead to a new cycle:

a. negative pituitary feedback of inhibin disappears
b. hypothalamic negative feedback of estrogen and progestin disappears
c. increase in the pulsatility of GnRH leads to an increase in the synthesis of FSH to rescue the follicles that began their growth 70 days before atresia.

**Endometrial changes.** The cyclic changes of the uterine mucosa are secondary to the events described in the follicle. Broadly speaking, during the follicular phase, the proliferation of all its components (glands,

stromal, and endothelial cells) stand out in response to the increasing follicular production of estradiol. Histologically, the increase in mitosis is striking and, thus, the endometrium grows in thickness from 0.5 mm at the end of menstruation to 5 mm at its peak, between approximately the eighth and 10th days of the cycle.

After ovulation, the increase in estrogen is compensated by the increasing effect of progesterone, which induces secretory changes in the epithelium, stromal edema, and increased spiral vessels. This secretory change reaches a peak between the 7 to 13 days postovulation, creating optimal conditions for embryo implantation. From a **histological** perspective, there are currently three zones are distinguished in the uterine mucosa:

a. a **basal layer** that has barely undergone histological changes and constitutes a quarter of its thickness
b. a **spongy layer** or central zone (approximately half its thickness) with very coiled vessels and dilated glands
c. A **compact stratum** or superficial zone with large and polyhedral stromal cells and congestive vessels. Körnchenzellen (K) cells, which are granulocytes with immunoprotective action necessary for implantation and placentation, are also detected. From this point, a process of decidualization begins in the endometrium, which will be completed in the event of pregnancy.

The decidua is the specialized endometrium of pregnancy, which will later be the mechanism that permits the "dialogue" between the fetoplacental unit and the mother. This is, therefore, an active organ from an endocrine perspective and the subject of ongoing research. In fact, the decidua produces an overwhelming and disconcerting amount of substances, some directly influenced by the production of estradiol and progesterone, but also has an auto and paracrine regulation that justifies its importance in human reproduction and in the pathophysiology of certain gynecological diseases:

a. It is responsible for creating access to nutrition for the embryo.
b. It suppresses the maternal immune response to favor embryonic invasion and produce new substances that will intervene in placentation (prolactin, renin, relaxin, insulin-like growth factor [IGF], IGF-binding protein).
c. Its periodicity is manifested in the substantial secretion of cytokines, which favor implantation or angiogenesis, such as GnRH (corticotropin releasing factor), leukemia inhibitory factor, or growth factor of the vascular endothelium; and others related to the reconstruction of a mucosa that will not support a pregnancy, such as prostaglandins, endothelin and haemostatic factors, all of which are involved in pathologies such as heavy menstrual bleeding or dysmenorrhea.

In the event that pregnancy does not occur, there is no GC that rescues and maintains the hormonal production of the corpus luteum. The endometrium then thins and becomes ischemic, presenting microhemorrhages and progressive necrosis that lead to complete desquamation of the two superficial layers. From that moment, the basal layer shows signs of regeneration to start a new cycle.

**Duration of the menstrual cycle.** The normal menstrual cycle results from a complex feedback system that involves the hypothalamus, the pituitary gland, the ovaries, and the uterus. In response to ovarian hormones, the endometrium undergoes cyclic changes, and at the end of each cycle, it is shed in the form of menstruation. It can be divided into a functional layer, which responds to hormonal stimuli, and a basal layer. Most of the changes that the authors have described in the menstrual cycle take place specifically in the functional layer.

The duration of the menstrual cycle depends on the speed and quality of follicular development during the follicular phase and varies between women both inter- and intraindividually. The average menstrual cycle in adult women lasts for 28 days, with a range between 21 and 35 days, with 4 to 6 days of bleeding and an average blood loss of of 30 mL, with 80 mL as the upper limit of normality. Only when the duration of the cycle exceeds this range or when the bleeding lasts for more than 7 days is this regarded as a reason for concern. Only 15% of women have cycles of 28 days and approximately 20% have irregular cycles (fewer than 21 or more than 35 days).

# 2. DISORDERS OF THE OVARIAN CYCLE: AMENORRHEA

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*Amenorrhea* is generally defined as the prolonged absence of menstrual bleeding. If the patient presents amenorrhea for the first time following menarche, this is called *primary amenorrhea*, a term also used to define a lack of menarche in teenagers over 16 years of age or when both menarche and thelarche, or development of secondary sex characteristics, are absent in a females 14 years or older. *Secondary amenorrhea* is much more frequent than primary amenorrhea and is diagnosed when a woman's menstrual cycle ceases for more than 6 months.

**Classification.** There are three main categories of amenorrhea: central (hypothalamus-pituitary), gonadal (ovarian), or genital (uterine-vaginal). In the same way, in the central and gonadal compartments, due to their different diagnostic and therapeutic implications, we will distinguish between organic causes and functional causes. Vaginal type amenorrhea is usually caused by imperforation of the hymen, and treatment (excision) can be administered at the time as of diagnosis. Uterine type amenorrhea is usually secondary to the destruction of the uterine mucosa via physical agents (curettage, radiation, hysteroscopic ablation), chemicals (quinacrine is used as a sterilization method in some countries), or infection (tuberculosis). When amenorrhea follows curettage, it is referred to as Asherman's syndrome. The diagnosis is made by hysterosalpingography or hysteroscopy.

**CENTRAL AMENORRHEA (CA)**

**A. Hypothalamic amenorrhea.**

**1. Organic:**

a. congenital deficit related to GnRh: Kallmann´s syndrome: Genetically transmitted; genetically transmitted disease (recessive autosomal inheritance, autosomal dominant, or related to chromosome X) characterised by an abnormal development of the GnRH producing neurons (hypogonadism) along with anosmia; alterations in the systesis of GnRH or the activation of the receptor, malformed lesions of the hypothalamic area (Prader-Willi syndrome, Lawrence-Moon-Biedl-Bardet syndrome)
b. destructive lesions of the hypothalamic area secondary to an injury that affects the area of the arcuate nucleus or its efferent pathways, altering the pulsatile secretion of GnRH (infectious processes, traumas, tumors, postirradiation)

**2. Functional:**

a. Physiological states (prepubertal and postpartum)
b. Iatrogenic, by drugs that produce an increase of prolactin (dopaminergic antagonist and opioids)
c. Weight loss
d. Systemic chronic diseases
e. Psychogenic: the liberation of corticosteroids and endogenous opiates decreases the pulsatility of GnRH, the cirulating GnRH, and the circulating

levels of gonadotropins (stress, depresion, exercise, malnutrition, anorexia nervosa, idiopathic)

**B. Pituitary amenorrhea.**

**1. Organic:**

a. cell and anatomical defects of the hypophysis: iatrogenic (postsurgery or irradiation); tumor related (adenomas of the hypophysis); empty sella syndrome; autoimmune diseases
b. hypothalamus-hypophysis vascular alterations: pituitary apoplexy; Sheehan´s syndrome: hypophysis necrosis, generally postabortion involving panhypopituitarism

**2. Functional:**

a. Secondary to hypothalamic pathology
b. Nonorganic hyperprolactinemia.

**Clinical.** Central amenorrhea's symptoms depend on the characteristics of hypestrogenism and the time of onset, and include the absence of menstrual bleeding. In patients with primary amenorrhea or those who are close to menarche, there may be signs of inadequate development of secondary sex characteristics. Since adrenarche precedes menarche and can exist without it, it is possible for patients with primary amenorrhea to have some axillary or pubic hair. It is also not uncommon to find a degree of breast development if the patient has sufficient adiposity. In secondary amenorrhea, symptoms are typical of estrogenic cessation.

**Hyperprolactinemias.** Although these are disorders of hypothalamic and/or pituitary origin that cause amenorrhea, hyperprolactinemias are studied separately because of their clinical significance and particular treatment.

**Etiology.**

1. physiological: pregnancy, breast feeding, sleep, mammary stimulation, exercise, sexual relationships, stress
2. pharmacological: dopamine D2 receptor antagonists: metoclopramide, domperidone, sulpiride, drugs that interfere with the synthesis or liberation of dopamine: reserpine, alpha methyldopamine. Hormones: estrogens, antiandrogens. Opiates, cocaine. Verapamil, Ranitidine
3. neurogenic: traumas or thoracic wall surgery, intercostal zoster herpes
4. association with other pathologies: primary hypothyroidism. Pseudocyesis. Chronic kidney failure. Liver cirrhosis. Adrenal insufficiency. Polycystic ovary syndrome
5. hypothalamic etiology: tumoral: craniopharingynomas, meningiomas, dysgerminomas. Granulomas: sarcoidosis, eosinophilic granuloma. Vascular: aneurisyms. Pituitary stem section. Cranial postradiation
6. hypophysis etiology: prolactinoma. Other secreting adenomas of the hypophysis: acromegaly, Cushing's syndrome. Nonsecreting adenomas of the hypophysis. Empty sella syndrome. Autoimmune hypophysis
7. idiopathic.

**Evaluation of a patient with hyperprolactinemia.**

Anamnesis: discard neurogenic, thyroid, or general pathology. Discard use of antidopaminergic drugs.

Clinical: Oligomenorrhea/amenorrhea. Galactorrhea. Loss of libido. Sterility. Headaches or visual alterations.

Complementary explorations. Biochemical: liver function. Thyroid function. Macroprolactin (in case of clinic-analytic discrepancy). Complete hormonal hypophysis (in case of hypothalamo-hypophyseal disease). Imaging study: magnetic resonance imaging (MRI) with gadolinium or CAT. Study of visual field. Bone mineral densitometry.

**Treatment of hyperprolactinemia.**

Only patients with clinical symptoms (oligomenorrhea/amenorrhea) and/or an associated microadenoma/macroadenoma will be treated. Medical treatment of choice includes surgery and radiotherapy as alternatives.

**1. Medical treatment of prolactinoma.** Treatment is recommended whenever prolactinoma is greater than 10 mm (macroprolactinoma), while microprolactinomas lower than 10 mm treatment depends on the clinic because 90% do not increase in size in 4 to 6 years. The treatment of first choice is with dopaminergic agonists prescribed by a general practitioner: CARBEGOLINE Cardiac alterations and valvular insufficiency can occur when used at high doses and over a long period.

**2. Surgical treatment.** Indicated when there is intolerance to medication, prolactinoma increase despite medical treatment, pituitary apoplexy, persistence of vision loss and/or neurological symptoms despite medical treatment, and pregnancy with neurological symptoms.

**3. Radiotherapy.** In the absence of a response to medication or surgery.

## FUNCTIONAL HYPOTHALMIC AMENORRHEA

Weight loss, intense physical exercise, or stress can alter the pulsatile secretion of GnRH. In addition, all three situations can coexist and be accompanied by eating disorders to varying degrees.

**A. Amenorrhea and weight loss** affects adolescents and young women: prevalence 0.5% to 1%. A loss of 10% to 15% of body weight can cause amenorrhea, particularly if it is rapid, the body mass index is less than 19, or there is low fat intake. Mediators: neuropeptide Y and leptin. Clinical: amenorrhea can be primary or secondary. The most serious situation is anorexia nervosa (restrictive or bulimic), a mental disorder that causes amenorrhea due to weight loss and is accompanied by florid symptoms of starvation and hypoestrogenism: severe malnutrition, hypotension, hypothermia, bradycardia, constipation, abdominal pain, and decrease of bone mineral density.

**B. Amenorrhea and intense physical exercise** affects 5% to 25% of elite athletes, particularly those in precompetition training, if weight is low, or if the diet is imbalanced or not supplying adequate nutrients. Mediators: leptin/sympathetic system (Interleukin 6 and catecholamines)/hypothalamic–pituitary–suprarenal axis activation. Clinical: hypoestrogenism; "female athlete triad:" amenorrhea + anorexia + athlete.

**C. Amenorrhea and stress.** Situations of physical or psychological stress, whether latent or evident, present or past, without malnutrition, psychiatric illness, or intense physical exercise, can cause amenorrhea or variable irregularities of the menstrual cycle. Stress factors: severely dangerous social situations, affective deprivation, and minor stress factors. Mediators: stress activates the hypothalamic-pituitary-suprarenal axis (HHS) with reduced corticotropin, reduced proopiomelanocortin, reduced adrenocorticotropic hormone, and reduced cortisol, which causes a reduction of GnRH and the subsequent reduction of LH pulses. The level of stress needed to activate the HHS axis is an individual characteristic, and it is unknown whether its basis is genetic or environmental. Clinical: neuroendocrine alterations that cause a bad response to stress (perfectionist, demanding, anxious attitudes, low self-esteem); eating disorders (particularly bulimia); other psychosomatic disorders (migraine headaches, irritable bowel syndrome, sleep disorders).

## TREATMENT OPTIONS FOR CA

### 1. With desire for reproduction

Approximately 20% of diagnoses of anovulation in infertility visits are due to CA (half of which are of hypothalamic-pituitary origin and the other half due to hyperprolactinemia). Etiological treatment should be pursued whenever possible because spontaneous recovery from amenorrhea has been recorded in 83% of functional hypothalamic amenorrhea due to eating behavior disorders or stress when the causative factor is corrected. Spontaneous recovery has also been observed in 29% of CAs of idiopathic etiology. Otherwise, a basic sterility exam will be completed and ovulation induction treatments or assisted reproduction techniques will be applied if necessary (artificial insemination [AI], in vitro fertilization [IVF], intracytoplasmic sperm injection [ICSI]). The hormonal requirements for these treatments are variable but always require a combination of FSH and LH.

### 2. Without desire for reproduction

**Prevention of osteoporosis:** work with patients toward achieving optimal bone mass using hygienic and dietetic measures, such as by encouraging a low-protein diet, adequate intake of dairy products and derivatives, increasing intake of calcium and vitamin D, and encouraging regular exercise. Patients should also refrain from smoking.

## SPECIFIC SITUATIONS

**1. Treatment of CA caused by physical exercise.** Extreme exercise carries greater risk of bone fractures due to overload and stress. Patients experiencing exercise-induced amonorrhea should receive early intervention, including periodic rest, reduction in the intensity of sports at the beginning of the menstrual cycle, dietary support with calcium and vitamin D supplements, and hormonal therapy (HT) in the form of contraceptives. The absence of regular bleeding patterns can be an advantage for athletes who want to avoid bleeding during competitions.

**2. Treatment of CA caused by eating disorders.** Patients with eating disorders should receive specialized and multidisciplinary care aimed at stabilizing body weight, providing nutritional education with family therapy, and treatment of any accompanying

psychological disorder, such as with antidepressants or neuroleptics. Patients with CA caused by eating disorders can receive HT in the form of nonoral contraceptives (vaginal or transdermal) so that their effectiveness is not affected by vomiting. Practitioners should advise patients on means of improving bone mass, and suggest that cyclic bleeding is a way to reinforce feminine identity as a treatment for distorted body image.

# 3. POLYCYSTIC OVARY SYNDROME

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Polycystic ovary syndrome (PCOS) is a complex and heterogeneous disease in which gynecological disorders coexist with metabolic problems in such a way that theories have been proposed to explain the pathophysiology of both processes. Updated diagnostic criteria were established in May 2003 during a global meeting of experts held in Rotterdam and have allowed for distinguishing phenotypes with different clinical manifestations. The new criteria are more generic and may have raised its already high prevalence; we have data to suggest that it is the most prevalent endocrinopathy in women, affecting 7% to 14% of women who are of childbearing age worldwide. This interest is two-fold; on the one hand, it helps in the correction of hormonal defects that cause hirsutism and ovulation associated with PCOS, and on the other hand, it prevents possible future complications linked to PCOS, mainly diabetes mellitus and cardiovascular disease (CVD).

The new criteria for the diagnosis of PCOS include:

- Presence of oligoovulation and/or anovulation.
- Clinical and/or biochemical signs of functional ovarian hyperandrogenism (FOH).
- Polycystic ovaries, which can be visually observed by ultrasound.

Although the definition seeks to unify the diagnosis of PCOS for inclusion in research projects, according to these criteria, four phenotypes have been established that will also help us to differentiate how we treat and follow up with patients with PCOS:

- Phenotype A or *classic* (FOH + anovulation + ultrasound criteria)
- Phenotype B or *classic without ultrasound criteria* (FOH + anovulation)
- Phenotype C or *ovulatory PCOS* (FOH + ultrasound criteria)
- Phenotype D or *PCOS without FOH* (anovulation + ultrasound criteria).

**Physiopathology.** PCOS is a process with a multifactorial pathogenesis. Like similar syndromes, PCOS comprises the combination of environmental and genetic (genome) factors that give rise to a complex and interactive network of components that define the risk for each individual. Genoenvironmental interaction has prevented the identification of specific genes that are directly related to the cause of PCOS. In addition, it is widely believed that genes involved in metabolic syndrome, chronic inflammation, and diabetes mellitus are candidate genes.

Although the pathogenesis of PCOS continues to be the subject of discussion in specialized forums, recent experimental studies have suggested that an intrauterine hyperandrogenic environment could be the basis for the development of many of the signs and symptoms of the syndrome. Classically, two theories based on FOH have been postulated: The first theory suggests that PCOS is caused either by an ovarian dysfunction, and the second suggests that its origins may be other endocrine processes such as hyperinsulinemia (CHI). Recently, numerous observational, epidemiological, and experimental studies have related the harmful stimuli that the fetus receives in key periods of its development with the appearance of certain illnesses in adults, whether metabolic, cardiovascular, neurological, or reproductive.

*Fetal programming* is the term used to define this hypothesis, and its effects may underlie immediate consequences such as abortion or growth retardation

as well as dysfunctions in the maturation of certain organs or systems. It is a highly epigenetic manifestation. *Epigenetics* refers to those inheritable modifications in gene expression that do not correspond to mutations in DNA, but to methylation and histone modifications. The fetal genome is particularly susceptible to these changes, and there is evidence that female fetuses may suffer a reprogramming of their development upon exposure to an androgenic intrauterine environment, thereby increasing the possibility of developing PCOS in the future.

PCOS is the most-studied gynecological disorder evaluated for possible fetal origin. In animal experiments, intrauterine androgens have reprogrammed the neuronal sensitivity to GnRH, modifying the gene expression of the oocyte that is responsible for abnormal ovarian development. Although many of these experimental data have not been confirmed in humans, the existing evidence leads us to suppose that PCOS could emerge in the context of fetal programming. Specifically, the intrauterine hypothesis is based on the notion that exposure to an excess of androgens produces an epigenetic phenomenon responsible for excess proteins belonging to the family of the transforming growth factor β (TGF β), including the Anti-Müllerian hormone (AMH).

An androgenic increase has also been observed in pregnant women between the 22nd and 28th weeks, later relating to the insulin resistance (IR), the CHI, the increase in the size of the ovaries, and the early menarche of their daughters. The mechanism responsible for this is not clear, as the placenta does not allow the passage of androgens from the mother to the fetus. For this reason, placental dysfunction in PCOS has also been suggested. Similarly, a tendency to have fetuses with growth retardation and low weight at birth has been observed in patients with PCOS, in which cases, as is known, from birth their adipocytes grow "as if trying to recover lost time," which increases obesity and IR and predisposes girls to PCOS.

**Clinical.** As we can see, FOH and IR are the clinical aspects of PCOS.

- Hyperandrogenism can manifest as hirsutism, acne, and androgynous baldness. In extreme cases, virilization may be observed with clitoral hypertrophy, breast aplasia, increased muscle mass, and a deep voice. Of these, hirsutism is the most common symptom (observed in 60% of women with PCOS). Its evaluation should be as objective as possible, using the Ferriman-Gallwey scale (a value greater than 8 is considered pathological). From a biochemical point of view, hyperandrogenemia is evaluated by measuring total testosterone, sex hormone-binding globulin (SHBG), and the free testosterone index (FTI: total testosterone × 100/SHBG).
- Even though insulin resistance is fundamental in the pathophysiology of PCOS, on its own, it has few clinical manifestations. When intense, it is associated with acanthosis nigricans (verrucous, velvety, and hyperpigmented lesions that appear in the folds of the skin, particularly in the nape of the neck, in the armpit, and in the submammary fold, caused by the mitogenic action of insulin in the basal cells of the epidermis). However, IR is responsible for long-term complications and those patients who become pregnant have elevated risk during pregnancy and delivery, mainly attributable to the increase in gestational diabetes. On the other hand, the prothrombotic state of the CHI can explain the recurrence of early abortions, which are more frequent in patients with PCOS.
- Anovulation: anovulation is a very frequent symptom caused by initially poor follicular development derived from an excess of androgens. Even in the prenatal period, the passage of primordial follicles to preantral and small antral follicles is accelerated, which causes an increase in the concentrations of AMH and difficulty in the action of the FSH. The excess of estradiol produced in these antral follicles is responsible for the reduction of FSH below the threshold necessary for follicular selection and dominance. In addition, it has been shown that patients with PCOS have an altered pulsatile pattern of GnRH, which causes an excessive secretion of LH. However, poor oocyte quality has not been found in patients with PCOS, and this is similar to that of normo-ovulatory patients when folliculogenesis is normalized.
- Obesity with a predominantly central distribution more commonly seen in males is present in 30% to 50% of women with PCOS, that is, the accumulation of visceral fat and a waist–hip index is greater than 0.85 (central obesity is the highest cardiovascular risk). Some authors have confirmed that being overweight or obese is not only a consequence of the metabolic alteration of PCOS, but that they are involved in an important way in its origin and maintenance. In fact,

adipocytokines regulate reproductive function and are related to an increased risk of IR and CVD, and thus, weight loss is essential to improve this endocrinopathy. Leptin has been the most studied adipocytokine and has been found to be elevated in patients with PCOS.

- Long-term complications: The polycystic ovary should be considered a health problem that goes beyond the reproductive sphere of women. Patients with PCOS have IR and CHI related to FOH. The probability of developing diabetes, obesity, dyslipidemia, and metabolic syndrome is higher in this group of women, which implies an increase in cardiovascular and oncological risk (endometrial adenocarcinoma), particularly in obese women. These risks have been observed by measuring indirect markers of CVD, including dyslipidemia, IR, and increased inflammation factors (C-reactive protein, homocysteine, leukocyte count). Studies have observed an increase in the thickness of the walls of the carotid arteries, excessive accumulation of calcium in the coronary walls, and endothelial dysfunction in women with PCOS. Although some of these alterations can be explained by obesity or IR, there is also an increased risk of CVD in thin or non-IR patients. In general, phenotypes A and B are those with the highest risk of CVD, which suggests that FOH can be considered an independent risk factor.

**Diagnosis.** A PCOS diagnosis requires a combination of 2 of the 3 symptoms characteristic of the disease:

***Disorder of the menstrual cycle ± clinical or analytical FOH ± ultrasound image***

This allows for classification into the four phenotypes: A, B, C, or D.

**PCOS ultrasound.** The existence of at least 12 antral follicles smaller than 9 mm or an ovarian volume greater than 10 mL are the ultrasound criteria for a polycystic ovary. These criteria must meet the following conditions:

1. The volume will be calculated according to the formula: 0.5 × length × width × height.
2. The size of each follicle will correspond to the average of both measurements.
3. It will only be necessary for the criteria to be met in one of the two ovaries.
4. It is not applicable in women who take oral contraceptives.
5. If there is a dominant follicle greater than 10 mm or a corpus luteum, the vaginal ultrasound should be repeated in the next cycle.
6. Ultrasound is performed in the initial follicular phase in women with regular menstrual cycles.

The "typical" image of a polycystic ovary is not exclusive to PCOS and can occur in up to 20% of normal women, in prepubertal girls, and in women with hypogonadotropic hypogonadism. Its mere presence is not, therefore, a diagnostic criterion, but it could be considered as a risk factor for PCOS, and we take it into account so that it is treated in a similar way in women who are going to be subject to assisted reproductive technologies (higher risk of ovarian hyperstimulation syndrome, abortions, and pregnancy complications).

**Treatment of PCOS in women without the desire to reproduce.** The treatment of patients without the desire to reproduce is aimed at alleviating or reducing the symptoms that accompany PCOS and the complications of IR:

**1. Combined hormonal contraceptives.** In women with signs of FOH, hormonal contraceptives with antiandrogenic progestin (cyproterone acetate or drospirenone) are the initial treatment of choice. Their mechanism of action is based on three points:

- the inhibition of the secretion of LH by progestin (which also prevents endometrial hyperplasia)
- an increase in SHBG produced by estrogen (which reduces the free androgen fraction, the biologically active fraction)
- suppression of adrenal androgen production.

With regard to which preparation to use, the contraceptives that carry cyproterone acetate have a more energetic antiandrogenic effect, since it inhibits 5α-reductase activity, thereby decreasing the availability of dehydrotestosterone, the most potent androgen. In general, to alleviate the signs of FOH, it is prudent to wait 3 to 6 months for the medical treatments to take effect, since the hair growth cycle lasts approximately 4 months. But in cases where the contraceptive has not managed to reduce hirsutism, we can resort to other specific antiandrogenic drugs that are detailed below.

**2. Antiandrogenic drugs.** The goal of this treatment is to decrease the level of androgens, inhibit androgen receptors, control the peripheral conversion of testosterone to dehydrotestosterone, or increase the transport protein (SHBG) to avoid excess free

testosterone: spironolactone, cyproterone acetate, finasteride, flutamide.

**3. Insulin sensitizer drugs,** mainly metformin, improve IR and reduce HI and the symptoms of PCOS, regardless of whether weight loss occurs. Although they produce improvements in almost all patients with PCOS, they are particularly effective in those with a diagnosis of IR or obesity (see *Gynecological infections related to reproduction [sexually transmitted infections]*). It has been suggested that a deficit of inositol could underlie PCOS. Myo-inositol hexakisphosphate, commonly known as phytic acid, is found in nature in wheat seeds, citrus fruits, nuts, and legumes, part of the vitamin B group, participates at the postreceptor level as a second messenger. Monogastric animals, including humans, have few phytases in their digestive system, and so inositol is metabolized primarily by the bacteria of the intestinal flora.

Although inositol is not an essential nutrient in our diet, consuming it can provide certain benefits. For example, inositol acts as a hypolipidemic agent in plasma, but it also has antioxidant properties that enable it to prevent the development of cancers and cell damage. In addition, it is hypoglycemic by delaying the digestion and absorption of starch, thus decreasing insulin need. At the reproductive level, inositol has been detected in the ovarian follicle and also appears to intervene in the meiosis of the oocytes. Few data exist pertaining to its deficit, but it has been observed that supplementing the diet with the galenic form of D-chiro-inositol has been associated with ovulations and spontaneous pregnancies. Currently, the results on the use of D-chiro-inositol are scarce, with the available studies only using small samples.

**4. Cosmetic treatments.**

1. transitory: For patients with mild hirsutism, local measures such as shaving or depilatory creams may be used.
2. permanent: Electrolysis/thermolysis or electric hair removal.
3. useful in treatment of seborrhea or acne: Although there is no evidence that clearly supports the relationship between androgenic levels and acne intensity, treatment with hormonal contraceptives or antiandrogens produces improvement of skin lesions and can be associated with other topical measures or conventional systems.
4. useful to treat androgenetic alopecia: The treatments are unsatisfactory; topical minoxidil has been shown to be effective in a small percentage of cases
5. useful to prevent complications: Despite the harmful health consequences associated with PCOS, most women are not aware of these risks. The early recognition and treatment of metabolic sequelae should be the main focus of healthcare for this group. Modifications of lifestyle, such as balanced diet, weight loss, and regular exercise, are of utmost importance. In the pharmacological field, drugs such as metformin seem promising in the treatment of cardiometabolic aspects.

Gynecological exams are recommended in cases of endometrial hyperplasia.

# 4. GYNECOLOGICAL INFECTIONS RELATED TO REPRODUCTION (SEXUALLY TRANSMITTED INFECTIONS)

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**Keywords:** Inflammation, leukorrhea, sexually transmitted infections, STIs

To prevent infections, the vagina has the following natural defense mechanisms: the physical barrier, composed of superimposed cell layers that, when combined in the process of renewal and regeneration, mechanically carry microorganisms found in their path. There are two types of antibodies in the vaginal mucosa: nonspecific and specific. The nonspecific are the IgA type and are responsible for identifying and eliminating all antigens in the mucosa, while the specific antibodies are of the IgG type and are secreted exclusively for each type of antigen. The endogenous flora (*Lactobacillus spp.*) create competition for space and the formation of lactic acid, producing a decrease in vaginal pH that prevents the growth of certain pathogenic bacteria.

**Genital infection** symptoms are associated with inflammation of the vulva and vagina and are typically accompanied by increased vaginal discharge (leukorrhoea). These types of infections are the most common among all women who consult for genital problems.

**Etiopathogenesis.** Physiologic causes of leukorrhea (vaginal or cervical secretions containing desquamated epithelial cells) may include normal processes in the woman's body, such as the hormonal cycle and sexual arousal, as well as periods of stress and the beginning stages of pregnancy. Sometimes leukorrhea is classified as pathological because it is abundant but without an infection or disorder. Other times, leukorrhea may be attributed to infectious causes (mainly candida infections or bacterial vaginosis) or noninfectious causes (use of tampons or condoms, cervical polyps and ectopia, tumors, cervical vaginosis, rectal vaginosis, or allergic reactions). Most instances of leukorrhea in women of reproductive age are physiological.

**Diagnosis.** Diagnosing patients with genital discomfort requires making a correct anamnesis. Gathering information about the patient's symptoms and sexual history can help to establish the patient's risk for STIs (see *Algorithm for the diagnosis of leukorrhoea*).

Clinicians may be able to diagnose leukorrhea based on symptoms alone, but diagnostic testing is advised (see *Overview of diagnostic tests for vulvovaginal infections*).

Along with an understanding of the patient's signs and symptoms, establishing the vaginal pH is helpful, along with the remaining tests indicated (see *Overview of signs and symptoms associate with most common cause of vaginal infection in women of reproductive age*).

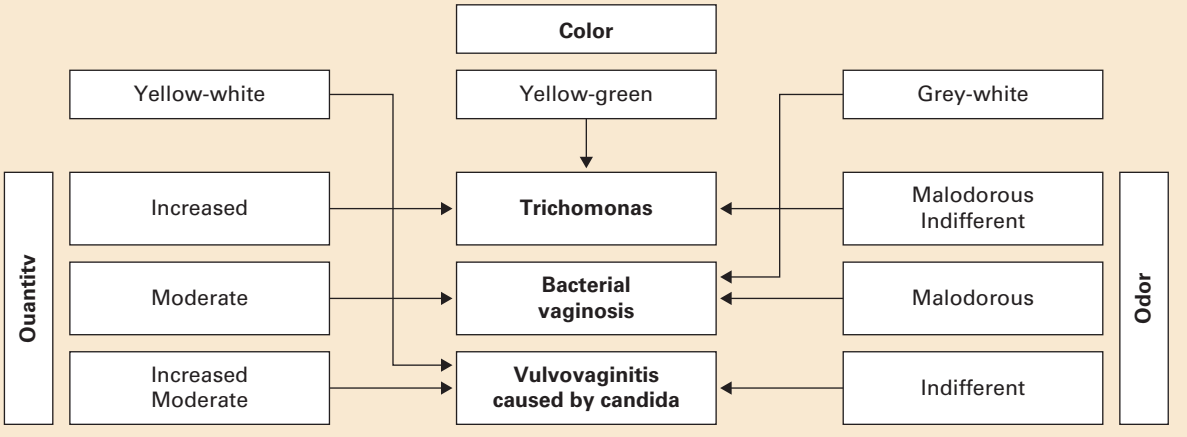
**Treatment.** The Health Protection Agency (United Kingdom) suggests that most women with leukorrhea due to bacterial or candida vaginitis, can be recommended for empirical treatment. As previously mentioned, empirical treatment is an option. The presence of pruritus makes *candida albicans* the most probable cause and appropriate antifungals can be prescribed.

If bad odor is present, bacterial vaginosis (BV) is the most likely cause and metronidazole is an appropriate drug for treatment.

**Treatment for bacterial vaginosis.** The recommended treatment for bacterial vaginosis is metronidazole. Neither testing nor treatment of sexual partners is indicated.

**Treatment of vulvovaginal candidiasis.** Oral and vaginal antifungals have identical efficacy in the treatment of vulvovaginal candidiasis. Vulvar antifungals (added to oral or vaginal treatments) may be used if the patient has local symptoms. Neither screening nor routine treatment of sexual partners is necessary. Patients should be advised that latex condoms, diaphragms, and cervical caps could be damaged by the use of certain vaginal antifungal treatments. Patients may use probiotics (such as bioactive yogurts) in the management of vulval candidiasis vaginitis or bacterial

## Algorithm for the diagnosis of leukorrhea




## Overview of diagnostic tests for vulvovaginal infections

| Specimen | Preparation | Detection |
|---|---|---|
| Pap smear (of side walls of the vagina) | Microscope and Gram stain | *Bacterial vaginosis*<br>Amsel criteria (3/4 present):<br>– whitish leukorrhea<br>– pH>5<br>– fishy odor (adding potassium dioxide solution to leukorrhea)<br>– Clue cells (vaginal epithelium cells surrounded by bacteria).<br>Nugent rating system by microscope exam of vaginal secretion smear stained using Gram´s technique. They are calculated rating the predominance of 3 types of morphology and bacterial stain. A rating of 7 out of 10 is consistent with bacterial vaginosis:<br>1. Gram-negative bacilli big (*Lactobacillus spp.*).<br>2. Small bacilli with variable Gram reaction (*Gardnerella vaginalis or Bacteroides spp.*).<br>3. Curved bacilli with variable Gram reaction (*Mobiluncus spp.*). |
| | Test wet mount | Trichomonas vaginalis (direct visualization of flagellated protozoa). |
| | Culture | *Neisseria gonorhoeae* (chocolate agar)<br>*Candida* (*Sabouraud agar method*) if the microscope test is not conclusive |
| | Awareness | In order to give the correct treatment. |
| Cervical smear | Culture immunological studies | *Neisseria gonorrhoeae*<br>*Chlamydia trachomatis* |

**Overview of signs and symptoms associated with most common causes of vaginal infection in women of reproductive age**

| | Bacterial vaginosis | Candida | Trichomoniasis |
|---|---|---|---|
| **Symptoms** | Fluent leukorrhea, malodourous or with fish smell<br><br>Associated symptoms: no itching | Thick, white leukorrhea, nonmalodorous.<br>Associated symptoms:<br>– Vulvar itching or pain<br>– Superficial dyspareunia<br>– External dysuria | Light or profuse leukorrhea, yellowish and foamy, malodorous.<br>Associated symptoms:<br>– Vulvar itching<br>– Dysuria<br>– Pain in hypogastrium |
| **Signs** | Leukorrhea surrounding the vagina and the vestibule<br><br>No vulvar inflammation | Normal findings or vulvar erythema, swelling, fissures, satellite lesions | Vulvitis and vaginitis<br>Strawberry cervix (only 2% of cases) |
| **Indicated test: vaginal pH** | ≥ 4.5 | < 4.5 | ≥ 4.5 |

vaginosis, but the evidence of its effectiveness is poor. Treatment failure (no resolution of symptoms in 7 to 14 days) is uncommon in vulvovaginal candidiasis, and the situation should be evaluated to clarify the causes of poor compliance.

**Treatment of vulvovaginal STIs.** The recommended treatment for *Trichomonas vaginalis* is oral metronidazole. Patients should be informed that *T. vaginalis* is a sexually transmitted infection (STI) and all sexual partners within the preceding 6 months should be notified and treated.

Patients identified as having an STI (*Chlamydia trachomatis* or *Neisseria gonorrhoeae*) should be treated in accordance with current national policies. Measures should be taken to diagnose other STIs and notify partners.

**Recurrence.** In cases of recurrent symptomatic leukorrhea, attention should be paid to the possible existence of other underlying causes. Clinicians should know that psychosexual problems and depression can be precipitated in women with recurrent vaginal infections. Appropriate advice should be given, and women should be advised to avoid douching, toilet gels, antiseptic agents, and shampoos in the bathroom. In recurrent fungal vulvovaginitis (four or more episodes in the last 12 months) an induction and maintenance treatment can be used for 6 months. Women should be advised to avoid douching, local irritants, scented products, and tight synthetic underwear. Recurrent trichomonas vulvovaginitis is usually due to reinfection, but the possibility of resistance to drugs should be considered.

**Sexually transmitted infection (STI).** The increase in the incidence of infections caused by sexually transmitted agents is a current public health concern. STIs are primarily transmitted by intimate contact. The microorganisms involved are particularly adapted to grow or penetrate through the genital tract.

**Patterns of STIs**

**Pattern 1.** The main manisfestation is a local injury, which can be insignificant (such as pubic lice) or constituted by genital ulcers, with the following characteristics:

- **Soft:** as chancroid, granuloma inguinale, lymphogranuloma inginale, and herpes
- **Excrescent:** such as injuries by HPV
- **Vaginal discharge without ulceration:** *Trichomonas vaginalis* and *Gardnerella vaginalis*

**Pattern 2.** Local injury, but more significant due to the possibility of spreading toward the reproductive tract, thus provoking pelvic inflammatory disease; gonorrhoea and *chlamydia trachomatis*

**Pattern 3.** Without (or minimal) local injury. The genital tract is only a channel for the systematic entry of a severe infection (for example, syphilis and infection due to HIV).

**Epidemiology.** The incidence of some so-called first-generation venereal diseases such as gonorrhea, syphilis, and chancroid has declined, particularly in industrialized countries, and they have been replaced by new bacteria and associated viral syndromes, mainly *Chlamydia trachomatis*, human papilloma virus (HPV), and HIV. These agents, considered second generation, are more difficult to identify, treat, and control, as they may be resistant to drugs and can remain latent or asymptomatic. Changes in sexual practices are difficult to promote, prolonged

adolescence, increased mobility of people, and socioeconomic factors are some of the most important epidemiological factors.

By definition, STIs affect both men and women equally, but their symptoms are often more pronounced in women. Generally, transmission is easier from man to woman than from woman to man through pathogens in the seminal fluid, the motility of the sperm, and the friction of the penis with the delicate vaginal mucosa.

**Patterns of STIs.** Most STIs manifest in three patterns (see *Patterns of STIs*).

Patients are often aware of the possibility of exposure to an STI, particularly victims of rape, or by participating a consensual relationship with a partner whose status is unknown or who does not know if they suffer from an STI. The possibility of contracting an infection from a single exposure varies according to its type, developmental status, and sexual practices. After sexual abuse, patients may be given an intramuscular injection of ceftriaxone, which can be effective in preventing trichomoniasis, chlamydia, gonorrhea, and bacterial vaginosis. Otherwise, the use of antibiotics is not recommended in a preventive manner.

# 5. GYNECOLOGICAL PROCESSES RELATED TO REPRODUCTION (ENDOMETRIOSIS, MYOMAS, POLYPS)

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**Keywords:** endometriosis, myomas, polyps

## ENDOMETRIOSIS

Endometriosis is a complex disease of uncertain origin and variable phenotype, and is a condition that underlies female infertility and pelvic pain. Defined as the "presence of ectopic endometrial tissue," its heterogeneity is also transferred to histology, with identification of endometrial glands and stroma being common. Other cellular elements can be recognized depending on the anatomical structure affected, which suggests that several pathogenic processes may lead to the same clinical disorder.

**Etiopathogenesis.** Despite its high frequency and clinical significance, the pathogenesis of endometriosis remains unknown. As with other complex illnesses, it is believed to result from a combination of environmental and genetic factors comprising a large interactive network that defines the risk and the clinical status of each affected woman. Because of its complexity, no specific gene has been identified that is directly linked to the onset of the disease. Many studies suggest that it does not manifest without the participation of an abnormal inflammatory response or without a peritoneal environment that contributes to the appearance of lesions on the endometrial tissue. Endometriosis behaves in some ways as neoplasms do: it invades adjacent tissues, can cause distant metastasis, and carries a higher risk of becoming malignant.

Several hypotheses have been postulated since the first clinical description of endometriosis. The three theories that correlate most with the usual presentations of the disease now prevail: retrograde menstruation in peritoneal endometriosis, vascular or lymphatic dissemination in distant endometriosis, and coelomic metaplasia in deep endometriosis. However, some lesions could be explained by a combination of these and all need to be complemented with an exam of the peritoneal environment in order to be fully understood. To further complicate its etiopathogenesis, the same endometrial cell, capable of its own implantation and *de novo* estrogenic production, has also been implicated to perpetuate the lesions beyond menopause.

Regardless of the way in which endometriosis is manifested, and independent of the underlying etiological cause, there is a clear dependency on hormonal stimuli, which explains its epidemiology and underlies certain therapeutic proposals. Thus, receptors for estrogen and progesterone have been isolated even in postmenopausal women and their lesions are maintained without estrogen stimulation from the ovary or fat because estrogenic *de novo* production has been detected. Some of the substances involved in the peritoneal environment (described in Table 1) have been linked to this local estrogenic production. As is common in its metabolic pathway, by autocrine and paracrine mechanisms, estrogen itself promotes the progression of the disease and the inflammatory response to it.

**Histology.** Histologically, endometriotic lesions have the same components as the eutopic endometrium: glands, stroma, fibrosis, and hemorrhage. The proportion of each varies depending on the location and age of the lesions. Thus, the early implants (those that are active) are shown as red lesions, while the older implants have moved to more or less pigmented and fibrotic areas. It has been agreed to refer to the former as atypical to distinguish them from the typical pigmented lesions of already established endometriosis. Consequently, this disease, which has been classically diagnosed by its appearance, has been based on the description of lesions that are unlikely to be active. For this reason, the diagnosis of endometriosis is as heterogeneous as the disease itself given the full range of presentations that must be considered.

**Types of endometriosis**

In **peritoneal endometriosis,** cells that come from retrograde menstruation are implanted. They commonly reach the peritoneum through transtube passage, although other routes of transmission (lymphatic and hematic) have also been described. However, retrograde menses do not completely explain the development of peritoneal endometriosis because they are often seen in women without disease and/or even in women without menses.

**Ovarian endometriosis** (**endometrioma**) can be derived from one or several implants of endometrial cells on the surface of the ovary or it can originate from the coelomic metaplasia of the invaginated mesothelial inclusions of the ovarian cortex. Defined by their ultrasound characteristics, we distinguish three types of endometriomas.

**Box 1: Mechanisms involved in favorable peritoneal conditions for endometriosis.**

- Increase of adhesion molecules (integrins and cadherins)
- Decrease of apoptosis phenomena
- Higher capacity to avoid local immune response
- Increase of the inflammatory response in peritoneal liquid: increase of leukocytes and macrophages, increase of growing factors and cytokines
- These growing factors and cytokines also increase adhesion and cellular proliferation and angiogenesis
- Decrease of the activity of natural killer cells
- Increase of metalloproteinase

- Type I: these show a homogeneous pattern with low echogenicity and thick wall, are the most frequently observed, and easiest to diagnose
- Type II: heterogenous
- Type III: homogenous and anechoic.

**Deep infiltrative endometriosis** can be formed from the endometriosis implants of the recto-uterine pouch, but they come preferentially from the coelomic metaplasia of Müllerian remnants that settle to this level and develop into adenomiotic nodules.

**Adenomyosis** is characterized by the existence of ectopic endometrial foci located in the myometrium

**Classification.** It is important to define the extent and location of the lesions in endometriosis. The most widely used classification guidelines were published by the American Society for Reproductive Medicine (ASRM). The classification assigns points to the size and depth of the implants and the severity of the adhesions and classifies patients into four grades:

1. Minimum endometriosis (less than 5 points)
2. Mild endometriosis (from 6 to 15 points)
3. Moderate endometriosis (from 16 to 40 points)
4. Severe endometriosis (more than 40 points).

This classification allows the inclusion of atypical lesions in the scoring system. However, it correlates poorly with the patient's reproductive prognosis and the extent of deep endometriosis. For this reason, other classification systems have been proposed, such as the Endometriosis Fertility Index that takes into account the surgical findings based on the classification of the ASRM, as well as factors related to the patient's clinical history that predict the possibility of pregnancy (the results vary between 0 for worse prognoses to 10 for better reproductive prognoses); or the Enzian classification, specific for deep infiltrative endometriosis, which is not yet very widespread and divides the severity into four degrees and into three locations (vaginal or gestational sac, uterosacral ligaments, or intestine).

**Uterine Myoma.** Myomas, also known as fibromyomas and leiomyomas, are benign tumors. They can be single or multiple and of variable size from microscopic to several kilograms in size. They are the most frequent solid tumors of the pelvis in women: one in four or five women of childbearing age have them. Their growth shows a clear dependence on female hormones, so they tend to grow during pregnancy and decrease during menopause. The classic pathogenic mechanism involves the formation of fibroids that resembles an oncological process. Family

history of uterine myomatosis is a risk factor for the development of fibroids, with a behavior that is different from nonfamilial myomas.

**Types of myoma.** There are several types of myomas: the submucosal type is a protrusion in the uterine cavity, the intramural types reside in the thickness of the wall of the uterus, and the subserosal type projects into the abdominal cavity. There are also cervical myomas that originate in the cervix. Each tumor usually has a major blood vessel.

**Clinical.** Many myomas are asymptomatic with any discomfort depending on their size and location. The most frequent symptoms include heavy menstrual bleeding (intramural) and irregular bleeding (submucosal). The intensity of bleeding can lead to hypochromic anemia. In addition, they can be a cause of infertility, miscarriage, dyspareunia, and diffuse pelvic discomfort. The mechanism by which fibroids have an adverse effect on reproduction is not clear, but the deformity of the uterine cavity and the vascular anomalies of the mucosa overlying the myoma could affect egg implantation. Myomas can cause pelvic pressure when the uterine size increases. If myomas compress neighboring organs, they can produce urinary symptoms or constipation and tenesmus by compression on the digestive system. The potential problems of these tumors during pregnancy are varied, with the most common being the increase in size and, eventually, pain. There may be a slightly higher risk of obstetric complications, such as miscarriage, premature delivery, abnormal presentations, and placental abruption. Occasionally, during pregnancy, myoma necrosis (red degeneration) can cause acute abdominal pain. During childbirth they can become pretumors, making it necessary to resort to a cesarean section because of the obstruction.

**Diagnosis.** A bimanual exam can detect the abnormal and irregular growth of the uterus. Ultrasound is the most effective complementary method, with 95% to 100% sensitivity, especially with vaginal probes. Hysteroscopy can aid in the diagnosis of submucosal localizations and may also be therapeutic. MRI is not a first-line technique, but it can be useful in cases of diagnostic doubt and to decide and plan conservative surgery (myomectomy) in young women who have a desire to reproduce.

**Treatment.** Approximately 40% of women with fibroids present symptomatology, so anticipatory management in the remaining patients is an obvious option, especially in women who are close to menopause. The main indication for starting the treatment is abnormal uterine bleeding that leads to anemia and alters the patient's life habits. Anovulators and intrauterine devices (IUDs) with levonorgestrel can reduce bleeding, but if bleeding persists and prior to surgery, GnRH agonists can be used. GnRH agonists can also be used in symptomatic perimenopausal women waiting to be treated as well as with patients expecting the natural onset of menopause.

Myomectomy is the surgical treatment (laparotomy or laparoscopy) of choice in patients who want future fertility or who want to preserve their uterus. Otherwise, hysterectomy is used and, depending on the particular conditions of each case, it will be conducted by laparotomy or laparoscopy and may or may not involve the removal of ovaries. Surgical hysteroscopy allows for the removal of submucosal fibroids. If patients are looking for a non-surgical alternative, minimally invasive treatments can be used, including embolization of the uterine arteries, which leads to a decrease in the volume of fibroids, achieving relief of symptoms.

**ENDOMETRIAL POLYPS.** Included within this term is any sessile or pedunculated formation inside the uterine cavity. Histologically, an endometrial polyp consists of glands, stroma, and vessels. There are polyps that undergo the same changes as the rest of the endometrium and others whose glands are inactive (meaning they do not respond to hormones). The possibility of malignancy is very rare. Endometrial polyps are often asymptomatic. If they appear, the main symptom is irregular uterine bleeding (usually scarce). Sometimes pain appears in hypogastrium. If there is no other apparent origin, they can be a cause of sterility. They can be observed by vaginal ultrasound and sonohysterography; however, hysteroscopy is the most accurate diagnostic method. Classically, they were removed by uterine curettage; today hysteroscopy with scissors or resectoscope is preferred if polyps are larger or their base of implantation is extensive.

# 6. FERTILITY AND STERILITY

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**Keywords:** fertility, infertility, reproduction health, sterility

*Sterility* is a generic term that refers to the problems that reduce human fertility and that, in the strictest sense, is considered a disease. From an epidemiological perspective, sterility is considered a frequent phenomenon. It is estimated that sterility affects some 70 to 80 million couples around the world, that 15% of those living in Western countries will consult for it, and that in these more advanced societies, there is a growing group of men and women who already have at least one child but wish to have another. There is a direct relationship between certain social and lifestyle factors and fertility and sterility: age; use of tobacco, alcohol, caffeine, marijuana, cocaine, and other drugs; use of anabolics; obesity; and psychological stress.

## DIAGNOSIS OF STERILITY

**When to diagnose sterility.** In the absence of previous indications, couples who have been trying to become pregnant for more than 1 year should begin testing and therapeutic measures. An exam should be conducted when the woman is over 35 years old or if there is a history of menstrual rhythm disturbances or suspicion of uterine, tubal, or endometriosis pathology, as well as when the male has a history of cryptorchidism or other testicular pathology.

**What is the basic sterility test?** This test consists of establishing a complete clinical history, a menstrual history, a general exam, preconceptional advice, and coital counseling. The exam must be given to both members of the couple. During the sterility test, cost-effective measures should be considered, being as minimally invasive as possible and conducted in accordance with the wishes of the two partners. The causes of sterility are varied and, in many cases, are multiple. This almost always involves both members of a couple. The tests included for sterility are gynecological exam and cytology, ultrasound of the uterus and ovaries, basic seminogram, tubal X-ray (hysterosalpingography), and hormone and ovarian reserve study serologies. In cases where another alteration is suspected and other fertility treatments have failed, other tests may be performed, such as advanced hormonal study, cervical or vaginal cultures, hysteroscopy, advanced seminogram and sperm DNA fragmentation test, and study of coagulation disorders.

**Monitored anamnesis in reproductive medicine.** For female patients, evaluation of anamnesis in reproductive medicine considers parity, obstetrical outcomes, age at first menstruation, menstrual formula, dysmenorrhea, contraceptive methods used, number of sexual relationships, length of sterility, results of EBE and previous treatments, previous surgeries and illnesses, gynecological history, allergies to medication, lifestyle habits (such as use of tobacco, alcohol, drugs, diet, and frequency of exercise), occupation (and any associated stress), and family history. For male patients, evaluate for STIs, obtain information about children from a previous partner (having other children does not exclude the potential for sterility), length of sterility and results from previous studies and treatments, previous surgeries and illnesses, medication allergies; lifestyle habits (such as use of tobacco, alcohol, drugs), occupation (and any associated stress), and family history.

**Diagnosis of ovarian function and the hypothalamic-gonadal axis.** Evaluate ovarian function, menstrual history, basal temperature, cervical mucus, serum progesterone, urinary LH, follicular development,

endometrial thickness and appearance; analysis of androgens, thyroid hormones, prolactin, and gonadotrophins. Conduct a transvaginal ultrasound.

**Study of ovarian function.** The evaluation of ovulatory function is an important part of the basic sterility test. However, we do not have any evidence that accurately assures us that ovulation has occurred except, obviously, pregnancy. This says a lot about the variability and false-positives of many of the tests that are routinely used in the clinic. A history of regular cycles corresponds to correct ovulation in 97% of cases.

**The test of the ovarian reserve.** Although age is the main prognostic factor of female fertility, in recent decades, motherhood has been possible for older women, which has changed our usual practice in the fertility clinic such that the analysis of the ovarian reserve has become one of the basic pillars upon which an adequate diagnosis and reproductive prognosis can be reached. Parameters for evaluating the ovarian reserve include biochemical markers such as FSH, E2, inhibins A and B, and, more recently, the AMH. Ultrasound markers include the ovarian volume, the number of antral follicles, and the flow of the uterine artery. In addition, some dynamic tests have been designed to improve the prognosis of those using drugs commonly used in ovarian stimulation (clomiphene, exogenous FSH, or GnRH analogues); these tests measure the variation of endogenous FSH, estradiol, and inhibin. Although they have been able to improve the sensitivity of the test, the increase is not sufficient to justify the expense and exposure to the established drug. AMH derives its name from its capacity to cause the regression of the conduits of Müller during masculine differentiation, but in women, the GC synthesizes these and has a great paracrine power. The mission of AMH is to inhibit the growth of nondominant follicles, with its local concentration increasing until reaching maximum levels in the antral follicles. Consequently, the measurement of AMH is a reflection of follicular activity, and as its peripheral blood values do not fluctuate as much as other hormones, it is used as an excellent ovarian reserve marker.

**Indicators of ovarian reserve.** Biochemical indicators of ovarian reserve include FSH, estradiol, inhibins A and B, testosterone, and AMH. Indicators observable by ultrasound include the number of antral follicles and the volume of the ovary. Dynamic tests may include clomiphene testing, exogenous follicle-stimulating hormone ovarian reserve testing, response of inhibin and E2 to exogen FSH, gastrin and serum testing, and testing the response of inhibin and E2 GnRH analogues. These various tests comprise the different ovarian reserve indicators. In summary, the most accurate are the ultrasound counts of antral follicles and the measurement of AMH; the least expensive are the ultrasound counts of antral follicles and the basal value of FSH and E2 (between the first and third day of the cycle); dynamic tests do not provide benefits compared with biochemical indicators or ultrasound tests and are expensive while remaining unable to predict the age of menopause presentation. Dynamic tests are only useful for offering a reproductive prognosis in women who plan to undergo fertility treatment.

## CAUSES OF STERILITY

**Ovarian factors.** The evaluation of ovulatory function is important as a first measure in basic sterility testing because it corresponds to 15% to 25% of the causes of sterility. A history of regular cycles corresponds to ovulation in 97% of the cases. A confirmed pregnancy is the only way to establish that ovulation actually occurred due to the great variability and false-positives involved with other tests. When an ovulatory dysfunction is diagnosed and a pharmacological treatment is indicated after 3 to 6 months without getting pregnant, another possible cause of sterility must be investigated. As a general rule, when the woman has regular cycles, ovulation is likely to be correct. When irregular cycles are presented we can measure progesterone in the second phase or request a graph of basal temperature.

A prolactin measurement routine is not necessary unless there are menstrual abnormalities, galactorrhea, or suspected pituitary tumor. Similarly, patients with anovulation have a higher proportion of presenting with thyroid disease, but thyroid-stimulating hormone will only be measured when this disease is suspected. The assessment of the ovarian reserve is made in certain cases of patients over 35 years of age or with the intention of providing them with a prognosis or additional information to decide on possible treatments. An FSH lower than 10 mIU/mL with E2 less than 30 pg/mL reflects a normal follicular reserve status.

**Cervical factor.** The cervical factor is a rare cause of sterility. The postcoital test is the classic test that determines it, but there is great interobserver variability, and it is not necessary to routinely carry this out because it has no prognostic value and is not

indicative of any type of therapy. Although uterine malformations are not usually a cause of sterility, examining the uterine cavity should be part of a basic sterility test. This should be done in an individualized manner, according to other previous findings, and should be based on a transvaginal ultrasound. In case of suspicion of organic pathology (polyps, submucosal fibroids, hyperplasia), a hysterosonography or a hysteroscopy will be requested.

**Tubal and peritoneal factor.** Tubal obstruction is responsible for infertility, either as a single cause or accompanied by other causes in 30% of cases. The tubal factor should be investigated when other sterility factors have been ruled out because the test that determines it, called the hysterosalpingography (HSG), is an invasive and often painful technique. Of course, if IVF or ICSI is planned, HSG is not needed. For the study of tubal factor, the HSG is the least invasive and most cost-effective form, allowing diagnosis of tubal obstructions (proximal or distal) and evaluation of the uterine cavity. It is done in the first phase of the cycle before ovulation. If screening for chlamydial infection has not been done, antibiotic prophylaxis must be carried out. However, it is not precise in detecting peritubal adhesions and for diagnosing a peritoneal endometriosis, in which case it is indicated to perform a laparoscopy if there are strong suspicions of endometriosis, tuboperitoneal adhesions, or important tubal pathology.

**Male factor.** The minimum evaluation of the male should include a complete medical history, a physical exam, and at least two semengrams separated 3 months from each other that should be initiated before subjecting the woman to any type of invasive exam, such as HSG. The seminogram is the main test in the study of the male factor, and abstinence is recommended for 2 to 3 days. The seminogram offers basic information on seminal volume, concentration, mobility, and sperm morphology. Unless the lab has its own criteria, it is recommended to follow the 2010 WHO guidelines.

## TECHNIQUES FOR ASSISTING REPRODUCTION

**What is artificial insemination (AI)?** Broadly speaking, AI involves the introduction of semen into the uterus, which is why it is also called intrauterine insemination. We distinguish the conjugal AI (CAI), meaning it is from the male partner, from donor AI (DAI). We have used the word "capacitated," which is an important part of this TRA. Indeed, for a sperm to acquire the ability to cross the membrane that surrounds the ovum and fertilize it, it must first undergo biochemical modifications in the most distal part of its head in a region called the acrosome. This phenomenon occurs naturally when the acrosome passes through the cervix and is imitated in the lab before being deposited inside the uterine cavity. Sometimes we use it as a diagnostic method known as a training test, and it helps us assess whether a patient's semen is valid for proposing a CAI.

**What are the indications of AI?** It can be supposed that all semen qualifies for CAI. In each clinic or unit of human reproduction, there are criteria to decide if the seminogram, as the analysis is called, is normal or has some alteration and also if it is valid or not for a CAI or even IVF or ICSI. Some centers have their own criteria for defining seminograms, and although few do, they must be centers where there is a researcher who has previously published such criteria in specialized journals. For this reason, the majority of reproduction labs use the WHO's criteria, which are periodically renewed. The latest revision is available online.

**What IVF and ICSI?** When IVF or an ICSI is proposed, the two gametes (oocytes and sperm) are needed in the reproduction lab to perform the fertilization, which is why it is called *in vitro*. According to the latest data collected by the Spanish Society of Fertility, the pregnancy rate per transfer is close to 40%. These techniques require the training and accreditation of the personnel in charge (gynecologists and embryologists) and are planned in a series of steps:

1. Follicular development: recruitment (rescue) and growth of one or more follicles, the structures of the ovary where the oocytes mature. Development is usually stimulated by a medication that contains gonadotropins, the natural female hormones responsible for follicular development. The process may be controlled with ultrasound and hormonal analysis.
2. Obtaining the oocytes. The vagina is punctured, and the process of obtaining the oocytes is guided by ultrasound. The follicles are punctured, and their liquid content (follicular fluid) is suctioned where the oocytes supernate. Although it can be performed under local anesthesia, sedation of the patient is preferred in many centers so that the patient does not suffer pain from the puncture.
3. *In vitro* fertilization. Fertilization itself occurs when the microinjection (ICSI) or its modern variant is

performed with the extension of the microscopic vision and the selection of the sperm with better morphology (intracytoplasmic morphologically selected sperm injection). This method currently accounts for three-quarters of in vitro fertilizations in Spain.

4. Embryo transfer (ET). Once the oocytes are fertilized, the resulting embryo or embryos are transferred into the uterus in a maneuver similar to that of AI. They are usually scheduled 2 to 6 days after the follicular puncture, and those that are not chosen for the transfer are cryopreserved for another attempt. The criteria to decide which are transferred and which are frozen are morphological, and each reproduction center usually has its own scale to catalog its quality. The number of embryos to be transferred is controversial and generates uncertainty in patients. The transfer of more than 3 embryos is not allowed and for ethical reasons it is often recommended to limit this to only one, although this restricts the percentage of pregnancies.

**What is preimplantation genetic diagnosis?** Preimplantation genetic diagnosis (PGD) was developed as a technique to find out the sex of embryos with a test that detects the Y chromosome in the selected embryonic cells. Evidently, the determination of sex is not the purpose of this technique, but rather its purpose is the location of genetic defects transmitted by the X chromosome. Since then, its use has expanded to other genetic diseases. Undoubtedly, the PGD has proved to be an extraordinary step, both for the knowledge of embryonic development and for the sterility and infertility clinic.

# 7. CONTRACEPTIVE ADVICE

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Since the introduction of the current term of "contraception," conceptual changes have taken place over the last few years. Family planning offers couples information pertinent to the possibility of choosing when to create a family and the number of its members. In this article, we discuss contraception and sexual and reproductive health. Most methods of avoiding pregnancy are aimed at controlling female fertility through the use of contraceptive methods, which can be used with or without family planning advice.

## CONTRACEPTIVE METHODS BASED ON FERTILITY KNOWLEDGE

While men are theoretically always fertile, a woman's fertility is limited to a few days of her monthly menstrual cycle. Overall, the combined fertility of a man and a woman is limited to 1 week of each cycle because only one ovulation occurs for each menstrual cycle. In the event that more ovulations occur, they would take place within a maximum interval of 24 hours because the secretion of hormones via the ovary will prevent new ovulatory events afterwards; after ovulation, the ovum is fertile for a maximum of 24 hours; sperm, under conditions of maximum fertility, do not survive for more than 5 days inside the cervix; all women have signs and symptoms that let them know if they are in a fertile or infertile phase.

**Signs and symptoms of fertility.** Each menstrual cycle begins on the first day of bleeding and ends on the day before the next menstruation. During this period a series of changes occur in the ovaries, creating observable physiological repercussions. Menstrual bleeding is the most obvious. Following this, the woman may notice that her genital area is drier (for instance, if a tampon is removed from the vagina, she may notice how it feels as though it is "scraping") before going on to feel more lubricated. This sensation is due to mucus secreted in the cervical crypts, and some may even see it in their underwear, during daily grooming, urination, or defecation. After a few days (varies among individuals), the woman may feel less lubricated. The last day of sensation of lubrication or the presence of mucus with fertile characteristics (clear, abundant, and transparent like egg white) is the peak day of mucus.

Patients can register all changes in the cervical mucus in a graph or app designed for this purpose, such as the one available at www.womanlog.com. If the woman wishes, she can record her basal body temperature 5 days after the start of menstruation using a thermometer placed below the tongue for 5 minutes or in the vagina or rectum for 3 minutes in the morning before getting up and having breakfast. The temperature should be recorded on paper or electronically in the graph designed for charting mucus. The woman can also register other signs and symptoms, such as abdominal pain, intermediate bleeding, mood swings, etc., all of which will help her to know how these are modulated by her cycle.

**Methods.** According to the WHO, any woman can use these methods based on the knowledge of fertility, provided that she learns to manage these properly. Recognizing the fertile phase of the cycle is also useful for couples who wish to conceive. Interrupted intercourse, traditionally considered a natural method, is not based on signs and symptoms of fertility, but rather is a barrier for sperm to not penetrate the vagina because the man withdraws when he perceives

the imminence of ejaculation, which he then completes outside the genital area of the woman. Its effectiveness is a function of the control that the man has over his ejaculation, and for some people, it is considered desirable due to its absence of effects on the personal and environmental ecology. Users of this practice should know that if a second bout of intercourse occurs very close to the first, the man will have to urinate and wash his penis to remove any seminal fluid that may remain on the glans or frenulum before penetration.

**Barrier methods of contraception.** Barrier methods of contraception are "pericoital methods," the use of which depends on the will and knowledge of the users. The only barrier method for men is the male condom; for women, the choices are diaphragm, cervical cap, female condom, vaginal sponges, and spermicides.

- **Spermicides** are chemicals that can prevent pregnancy if they are used correctly and consistently. With typical use, they provide much less protection against pregnancy than with when they are used optimally. The failure rates of spermicides during the first year of use vary between 6% with perfect use to 21% with typical use. Its mechanism of action is the immobilization and destruction of sperm in the vaginal cavity. Products based on the spermicide Nonoxynol-9 (including condoms containing spermicide) are not advised for the prevention of HIV and STIs or as contraceptives in nonmonogamous couples due to the increased risk of HIV infection, AIDS, or other STIs due to the microlesions they produce in the delicate vaginal mucosa.
- There are several types of **diaphragms,** which are manufactured with rubber or silicone. They are shaped like a bowl with a ring on their edge so that they can be fixed in the vaginal cavity. They act as a barrier and as receptacles to keep the spermicide adhered to the external cervix. Failure rates are between 6% and 18% and are largely attributable to misuse. The diaphragm is folded into the vaginal fundus, and there it unfolds and is confirmed to cover the cervix with support from its anterior part in the retropubic fossa. For removal, the reverse pathway is followed by pulling with the index finger.
- **Cervical cap.** Made of silicone, it is designed to fit the cervix by suction, providing a partial mechanical barrier to sperm passage.
- **Male condoms.** Manufactured from latex, animal intestine, polyurethane, or Tactylon, male condoms can be lubricated or nonlubricated, smooth or finished at the tip, and may include a reservoir for semen. Their use prevents all STIs, although natural or animal intestines do not prevent the transmission of viral infections, including HIV. Selecting the correct width can reduce the breakage rate. Latex condoms deteriorate and lose efficacy after 1 hour of exposure to mineral oils, baby oils, petroleum jelly, olive oil, peanut oil, corn oil, sunflower oil, palm oil, margarine, coconut oil, butter, insect repellents, anti-hemorrhoids, vaginal creams with estrogens, spermicides, and some sexual lubricants. It must be put on after the erection and before any genital and/or anal contact. HIV is present in the pre-ejaculate in the case of seropositive men, being able to transmit the infection. In the figure below, the behavior to be followed in case of condom breakage is summarized.
- **Female condoms.** These are polyurethane sacks, which, once inserted, cover the vagina and the cervix.

**IUDs.** This form of contraception has been available for the last 40 to 50 years. It works by placing a progesterone-releasing device inside the uterine cavity. IUDs are manufactured with plastic materials, sometimes with the addition of a copper spiral. Approximately 6% of women of childbearing age currently use this method because it is highly effective with few side effects and a high rate of continuity of use. Women desiring a long-term method of contraception who do not have heavy menstrual bleeding often choose a copper IUD. It is a method that has no adverse systemic effects. The levonorgestrel-releasing IUD preserves the basic elements of the so-called T-shape, horizontal branches, vertical branch, and guidewires, but a reservoir has been added to the vertical axis in which levonorgestrel has been placed.

**Mechanism of action.** There is no conclusive scientific evidence regarding the mechanism of action of IUDs. In recent years, several hypotheses have been proposed: in response to a foreign body, the local inflammatory reaction produces an increase in capillary permeability, endometrial edema, and an increase in the presence of macrophages that exerts an antisperm and anti-implantation effect; copper-releasing IUDs could hinder fertilization by acting as gameticides and, fundamentally, spermicides; levonorgestrel-releasing

IUDs cause the endometrium to be hostile to sperm migration, along with the alterations it induces in the cervical mucus, making it impermeable to the penetration of sperm; the action of IUDs is preconceptive and is unlikely to interfere with implantation.

**Preinsertion requirements.** Inform and advise on the method itself and its possible side effects (pain, bleeding, etc.). Make a general and gynecological anamnesis to rule out risk factors and contraindications. Conduct a basic gynecological exam. Additional complementary tests, including cytological screening, are not needed. The IUD can be inserted on any day of the menstrual cycle, and not only during menstruation days. The administration of a nonsteroidal anti-inflammatory drug one hour before insertion may be useful.

- Postinsertion checks, IUD replacement, and withdrawal. A first check during the 3-month period postinsertion is advisable but not essential. This is to confirm that the threads of the IUD protrude through the external cervical os.
- Postoperation sonographic checks are not necessary.
- Subsequent checks should be scheduled according to the age of the woman.
- In the event of fever of unclear origin, lack of menstruation, pelvic pain, pain during intercourse, increased vaginal discharge, or irregular bleeding, the woman should seek medical advice.
- The effectiveness of IUDs is related to copper loading, and the levonorgestrel-releasing IUD is considered more effective.
- Hormonal IUDs with a copper surface of 380 mm (high charge) can remain inserted for up to 10 years in some models.
- In women under 40 years of age, replacement of the IUD is advised after 5 or 10 years, whereas in women over the age of 18, the IUD can remain inserted until menopause without needing replacement.
- The appearance of pelvic inflammatory disease in a woman who has inserted an IUD is not an indication for withdrawal and can be treated without further action.

**Female sterilization.** Female surgical contraception or tubal sterilization (TS) is the most effective contraceptive method, used by approximately 21% of women over age 45. The percentage of pregnancies following TS is around 0.4% to 0.5%, either due to failure of the method itself or due to technical errors. A third of these pregnancies will be extrauterine. TS is performed at the woman's own request as a form of permanent contraception. In certain cases, there may be a medical indication (for instance, risks from a new pregnancy in women with previous obstetric complications or in carriers of genetic diseases that are transmissible to the fetus).

**Prior advice.** TS should be described alongside other alternative contraceptive methods so patients can make informed and voluntary contraception choices. TS is a simple, safe, and permanent method of contraception. Patients who request this procedure must be informed about the techniques to be used as well as their possible complications. The risks of anesthesia (if any), surgery (if any), and the possibility of failure of the method should be explained before the intervention. Under no circumstances should TS be considered a form of temporary contraception. Surgical TS is effective from the moment it is performed and does not require evidence of permanent motivation; however, a waiting period of about 3 months is required for modern mechanical methods. At the end of counselling, the woman must sign an informed consent document stating she understands that the procedure is final and irreversible.

**Tubal sterilization techniques.** Surgical techniques for TS include abdominal access via laparotomy, minilaparotomy, or laparoscopy; vaginal access through the posterior vaginal fundus (this method is the least used), or transcervical access via a hysteroscope. Procedures using the chemical quinacrine are used in some developing countries but are the least recommended.

The most commonly used methods include simple ligation by minilaparotomy using the Pomeroy, Irving, or Uchida technique or fimbriectomy; laparoscopic bipolar electrocoagulation; and tubal occlusion using clips from Hulka, Filshie, or Yoon rings, generally placed laparoscopically. In all cases, the intervention can be performed under local or general anesthesia.

# 8. HORMONAL CONTRACEPTION

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Combined hormonal contraceptives (CHC) are drugs composed of an estrogen and a progestogen, which can be administered through different routes. The fundamental mechanism of actions in CHC drugs are the inhibition of ovulation, the thickening of cervical mucus, and the alterations in endometrial maturation. Almost all the commercialized CHC formulations contain the ethinylestradiol estrogen at a dose ranging between 35 and 15 mcg daily. More recently, estradiol valerianate has been introduced. The progestogen content of CHCs differs by product, and the differences lie in the hormone's ability to interact with androgen, glucocorticoid, or mineralocorticoid receptors. Hormonal medications used in CHCs include:

- cyproterone acetate, with potent antiandrogenic activity, which is currently used exclusively for the treatment of acne, hirsutism, and hypertrichosis
- levonorgestrel, a second generation of progestin, whichhas mild androgenic activity
- gestodeno, desogestrel, and norgestimate, which are third generation progestins and have less androgenic activity with which other side effects are associated
- drospirenone, with a marked antiandrogenic activity, which has been linked to an increased risk of thromboembolic traumas.

**Routes of administration.** CHCs can be administered in five ways:

- oral route in the form of a combination pill or a progestin-only pill
- parenteral route in the form of injectables with depot medroxyprogesterone acetate
- transdermal route in the form of patches and implants
- transvaginal route in the form of vaginal rings
- iIntrauterine route: in the form of levonorgestrel-releasing intrauterine systems.

**Prerequisites for CHC prescription.** Before prescribing CHCs, conduct the following:

- carry out a careful clinical history to rule out risk factors
- take BP
- increase the likelihood of the continuity of injectable usedispelling any fears about CHC use the patient may have
- avoiding unnecessary medical rituals (for example, no routine genital exam is necessary before prescribing)
- working with patients to overcome resistances to administration routes (for example, taking pills, getting injections, inserting rings, applying patches, etc.).
- help women choose, offering possibilities, and letting them decide what best suits their needs.

**Eligibility criteria.** According to the WHO, there are situations in which CHCs should not be used for any reason because they fall within Category 4 of their eligibility criteria. As we can see in the table below, most cases affect problems related to hypercoagulable states of the blood, since it is known that combined hormonal contraceptives have a thrombophilic activity.

## WHO ELIGIBILITY CRITERIA

### Category 4

CHC use is contraindicated if the patient:

- is within the first 6 weeks of breastfeeding
- smokes more than 15 cigarettes per day and is over 35 years old

- has a history of breast cancer within the past 5 years
- has a personal history of deep vein thrombosis or pulmonary embolism
- has been diagnosed with family thrombophilia or shows thrombogenic gene mutations
- has a first-degree relative with venous thromboembolism diagnosed at younger than 50 years while studying whether family thrombophilia exists
- has thrombophilia acquired through prolonged immobilization and abdominal or trauma surgery
- has diabetes mellitus associated with vasculopathy, neuropathy, or nephropathy for more than 20 years.
- has a history of stroke or cardiovascular disease or multiple risk factors for cardiovascular disease
- has migraine headaches with aura
- has active liver disease or liver conditions, including hepatitis, cirrhosis, adenomas, or carcinomas
- has high BP (systolic greater than 160 mmHg or diastolic greater than 100 mmHg).

Although the risks outweigh the benefits, its use could be considered only when there are no other options available. Other clinical aspects, which are included in Category 3, are related to the prevention of cardiovascular events, and among these puerperium and smoking play a relevant role. **Category 3.**

- breastfeeding between 6 weeks and 6 months postpartum
- immediate postpartum (first 3 weeks)
- smoking of less than 15 cigarettes per day in people over 35 years old
- systolic BP of 140 mmHg to 159 mmHg or diastolic BP of 90 mmHg to 99 mmHg.
- previous history of breast cancer (within the past 5 years)
- hyperlipidemia
- migraines without aura in women over 35 years
- current active vesicular disease
- history of cholestasis associated with prior use of CHC
- compensated liver cirrhosis
- use of drugs such as rifampicin or anticonvulsants.

In all other situations, either there are no restrictions (Category 1) or the advantages outweigh the risks (Category 2).

**Controversies.** The risk of thrombophilia in users of combined hormonal contraception is a recurrent problem in the literature. Thromboembolic disease is a serious but rare condition affecting women of reproductive age. According to the Royal College of Obstetricians and Gynecologists, the absolute risk of developing venous thromboembolism in non-user women versus users is as follows: Women of reproductive age: 4 to 5/10,000 women/year. Users of AHC: 9 to 10/10,000 women/year. Pregnancy: 29.4/10,000 women/year. Immediate post-partum: 300 to 400/10,000 women/year.

In users of CHC pills, the risk of venous thromboembolism rises between 35 to 99 times if they are carriers of the Factor V Leiden mutation, especially during the first year of use. This risk seems to be greater in users of pills containing desogestrel or gestodene. The risk of venous thromboembolism in carriers of protein C deficiency and antithrombin deficiency increases between 2 and 9 times, respectively. The safety of contraceptives that contain only progestogens in hypercoagulable states is unknown. The accumulated data also indicate that women older than age 35 years, smokers with hypertension, and women under age 45 years suffering from migraine with aura may be at higher risk.

While studies have not demonstrated differences in the efficacy of ultra-low estrogenic doses compared with low doses, there is some risk in discontinuation for ultra-low doses. This is because ultra-low estrogenic doses increase the risk of bleeding disorders, including menorrhea, prolonged bleeding, or irregular bleeding, which are poorly tolerated by users. Information is limited for so-called "new" progestins, such as drospirenone, an analogue of spironolactone with antimineralocorticoid and antiandrogenic activity. It is contraindicated in patients with renal failure, hepatic dysfunction, and adrenal insufficiency, and should be used with caution in women taking potassium supplements, diuretics, and heparin. Its safety and efficacy profile is similar to that of other preparations, and despite the temporary weight loss in the first 6 months of use, body weight returns to similar or slightly higher levels to that recorded before treatment.

**Combined oral hormonal contraception (COHC).** In COHC there is no single method that is better than another. The acceptability of each one depends on the expectations of the woman and her tolerability towards its side effects. There are various types of preparations on the market, with different dosages and hormonal combinations. For practical purposes, they are classified according to:

- whether the pills have the same composition or not: they would be prepared as monophasic, combyphasic, or triphasic

- the dose of estrogen (15, 20, 30, 35, 40/30 or 50 mcg) per pill
- the type of progestogen contained (cyproterone acetate, levonorgestrel, gestodene, desogestrel, drospirenone, chlormadinone acetate, norgestimate, or dienogest).
- the number of pills in each blister (21, 22, or 24, interspersed between a few days without a pill when hemorrhage occurs due to withdrawal, or with 28 tablets for continuous daily intake, in the form of a blister with a certain number of placebo tablets).

**Dificulties with the use of COHC.** For users, the daily ingestion of the COHC pills causes some difficulties. On average, each woman forgets to take at least 1 pill per cycle and more than 50% forget more than 3 pills by the third cycle of use. Another problem is the high discontinuation rate (which during the first year of use could reach 60%), as well as incorrect and inconsistent use, which lead to a large number of unwanted pregnancies. Between 60% and 81% of those who interrupt COHC do so because of its side effects: bleeding outside of the time expected for withdrawal bleeding (which most women tend to identify as menstruation), nausea, perception of weight gain, mood swings, breast tenderness, and headache. When COCH pills became available in the 1950s, women began taking them in the first 5 days of the menstrual cycle. Recent studies have shown that the so-called "Quick Start Method," in which the woman takes the first pill of the regimen on any day of the cycle after ruling out pregnancy, can be recommended. Another innovation is to indicate what is called the "extended or prolonged oral contraceptive cycle," in which 84 days of administration of a combined levonorgestrel/ethinylestradiol pill is followed by 7 days of placebo pill intake, with only 4 bleeds per year compared with the usual 13.

**Transdermal contraceptive hormonal patch.** Another COHC route of administration is a percutaneous patch. Its mechanism of action is similar to that of oral hormonal contraception, inhibiting ovulation, and thickening the cervical mucus. Each patch should remain stuck on the skin for 7 days, requiring weekly application for 3 consecutive weeks, leaving 1 week free of patching to induce withdrawal bleeding. Patches can be applied to the chest (but away from the breasts), the lower part of the abdomen, the upper part of the arm, or the buttocks. The users continue their daily activities, including exercise, bathing, and showering. No lotions, makeup, or any other substance that may interfere with the absorption or adhesion of the patch should be applied to the area.

**Vaginal contraceptive ring.** This is a system of intravaginal release of ethinylestradiol and etonogestrel (a derivative of desogestrel). Women who start using it will insert the first ring during the first 5 days of the cycle and will replace it every 3 weeks, leaving a week free of the ring if they wish to have withdrawal bleeding, or withdrawing a ring and inserting another one in case they wish avoid it. Its mechanism of action, similar to that of the rest of the combined methods, is inhibition of ovulation and thickening of cervical mucus.

The contraceptive efficacy of the vaginal ring is high. The failures of the method derive from forgetting to replace the ring, removing it during intercourse and not inserting it until after more than 3 hours, and using it after its expiration date. With the 3-week use schedule, withdrawal bleeding is induced in 97% of the cycles, and there is irregular bleeding in 6.4% of the cycles. Its contraindications are identical to those of the other forms of COHC. The adverse effects most frequently related to the use of the vaginal ring are intercalary bleeding (6.4%), vaginitis (13%), headache (11%), and leukorrhea (5.9%). Its advantages are that it is easy to use and discreet, that it has a low estrogen dose release, and it has optimal compliance. Among its drawbacks, the most important are its economic cost, the need to overcome the repulsion factor by introducing something into the vagina, and its availability. Its side effects are similar to those of the other types of COHC.

**Contraception with gestagens only.** Contraception with only progestins can be provided by different routes: oral, subcutaneous, injectable, intrauterine, or vaginal. We have progestogen-only pills (also known as minipills), which contain only desogestrel, a quarterly injectable medroxyprogesterone depot, a subcutaneous implant (etonogestrel ), and an intrauterine system that releases levonorgestrel. The main disadvantage of contraception using only gestagens, whatever their route of administration, is the poor control of uterine bleeding, producing irregular and unpredictable bleeding along with amenorrhea due to endometrial atrophy, both of which lead to a high discontinuity rate.

**Emergency contraception.** Emergency contraception (EC) means the use of a drug or device to prevent pregnancy after unprotected intercourse or when the

method in use has failed. Emergency contraception can be performed with progestins, IUDs, and selective modulators of progesterone receptors (ulipristal acetate). EC with only progestins consists of the administration of 1.5 mg of levonorgestrel before 72 hours postintercourse. It has few side effects, with nausea in 23% of cases and vomiting in 6%. Its effectiveness ranges between 49% and 85%, depending on the hours that pass until its administration.

This pill, and in general all progestins, has a fundamental mechanism of action to inhibit or delay ovulation. One tablet is also available with 30 mg of ulipristal acetate, a selective modulator of progesterone receptors, which acts as a nonhormonal emergency contraceptive. It can be administered up to 120 hours after intercourse. Its mechanism of action makes it susceptible to act even when ovulation is imminent or has already occurred because it eventually interferes with the progesterone receptors of the corpus luteum. The copper IUD as an emergency contraceptive has been used for a long time when the period in which levonorgestrel is effective has exceeded. EC's mechanism of action is to decrease the quality of the ovule, inhibit implantation, and reduce the amount of sperm that reaches the fallopian tubes and its fertilizing capacity. Its effectiveness is higher than 95%.

# 9. SEXUALITY DURING PREGNANCY AND POSTPARTUM

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Historically, in Western cultures, pregnant women have been considered as "asexual," lacking in sexual desire and activity during pregnancy and in the weeks and months after delivery. Sexuality is often ignored in dialogues between healthcare providers and pregnant patients, or arbitrary periods of abstinence are imposed on these patients, and the indications regarding sexual activity in these periods are rarely clear or explicit. All this can lead to a state of confusion and anxiety that can significantly limit or eliminate sexual contact with the partner, generating feelings of guilt. Both situations can alter couple relationships, not only during pregnancy and the puerperium, but also for a long period thereafter. Sexuality undergoes important modifications throughout the life of women. Pregnancy is a dynamic period with many changes in its evolution, and the same happens in the puerperium. They are two stages of life that generate profound changes in sexual function and must be recognized in order to adopt an adequate approach and give appropriate counseling to the couple.

**Can sexual relations during pregnancy endanger the fetus?** There is great variability in the results of studies. The activity of intercourse during pregnancy can endanger the health of both the pregnant woman and the fetus, while others argue in favor of the benefits that sexual activity can bring during this period, linking it, among other things, to psychological factors. Changes in sexual behavior are frequent and begin soon after conception. The direction and intensity of these changes are subject to great individual variations rather than certain regularity. It is likely that these variations are related to factors such as the psychosexual development of the woman, her personality, personal history, and the type of relationship with her partner and the impact of pregnancy on her health. The decrease in sexual desire and coital frequency has been confirmed to be determined by factors such as fear of damaging the fetus, decreased libido, somatic factors, or difficulty in the coital position, although there is less impact on multiparous women due to previous experience.

The first trimester of pregnancy is usually accompanied by a decrease in desire and sexual activity in general. Initially, the sexual response of women is vascular, and in pregnancy, an increase in vascularity occurs. In the first trimester, women experience changes in smell, psychological states, etc. There are no standard criteria regarding the changes that occur in the second trimester. In many studies, an important decrease in the sexual activity of women is observed, which eventually has an impact on the couple, whereas in others, it has been found to have the opposite effect. In the third trimester, a marked decline in sexual response and coital activity occurs in almost all pregnant women in most of the studies conducted. All these modifications are intimately related to the physical and psychological changes experienced by the pregnant woman.

**Does sexual desire change in a couple expecting a child?** Pregnancy induces vascular, muscular, and neurological changes that affect sexuality. However, we

can affirm that, thanks to these changes, the woman's libido increases during her pregnancy. The vagina, in addition, increases its flexibility and lubrication, and the breasts become more sensitive. However, it is not surprising that pregnancy is not perceived well in advance and that sexual desire decreases during the first trimester due to the fatigue, breast tenderness, and nausea typical of this period. Women often lose sexual interest close to the time of delivery because of abdominal volume and fears about the impending birth. Because the pregnant woman is often attractive to the male and sex reinforces the affective bonds without damaging the fetus (oxytocin is released but in insufficient quantities to cause uterine contractions), almost all of the pregnancy is suitable for sexual relations.

**When can sexual relations be resumed postpartum?** In general, it is recommended to restart sexual relations only after the episiotomy (if carried out) has completely healed. It is also recommended to wait until the pelvis returns to its prepregnancy state, so it is prudent to wait 3 or 4 weeks after delivery to resume sexual relations, which is the time needed to consolidate these processes. In any case, it is recommended that before resuming sexual relations the woman attend a puerperal check-up, so that the doctor or the midwife can confirm that everything is going well and that there are no problems with sexual practice. Vaginal dryness caused by the decrease of hormones following childbirth is normal while the woman is breastfeeding or until her period returns and can cause discomfort in sexual practice. To avoid these discomforts, oils and lubricating creams can be used until the natural lubrication of the vagina is recovered. Some women, when resuming sexual relations after childbirth, feel pain, which they had never experienced before becoming pregnant. If this happens, the woman should consult her doctor, since this could occur for several reasons, including poor healing of the episiotomy, fear of becoming pregnant again, etc.

**Restrictions on sex during pregnancy.** The most recent discussions about the risks of sexual activity during pregnancy focus on intercourse. One caution is that intercourse can promote infections such as amnionitis, which can induce premature rupture of membranes and premature delivery. All of these possible risks derived from sexual activity during pregnancy are still controversial today, which suggests that it is necessary to conduct more research on these issues to provide clearer and more objective data. The classic recommendation has been sexual abstinence 1 month before and 1 month after giving birth. Most current obstetrics manuals recommend not modifying or interrupting sex habits during pregnancy as long as they are not uncomfortable. When the abdominal volume becomes considerable, intercourse with certain postures can be very uncomfortable. In this case, more comfortable positions can be adopted, such as the lateral position.

More attention should be paid in the event of genital hemorrhage, threatened preterm delivery, or rupture of membranes, cases in which intercourse is contraindicated. Normally, and in general, sexual intercourse is discouraged in the last 2 to 3 weeks of pregnancy based on the probable date of delivery. Once delivery occurs, the resumption of sexual intercourse is determined by multiple factors, such as vaginal discharge, scarring of the episiotomy, etc. A period of coital abstinence of about 3 to 4 weeks is usually recommended, although individual attention should always be provided for each case.

**Contraception postpartum.** If breastfeeding is the only food that the baby receives, and the hours of required feeding are met, it is probable that the woman does not ovulate and, consequently, does not menstruate. This contraceptive method is called lactational amenorrhea method, but it is highly insecure so the couple must take other contraceptive measures if they have sex and do not want to become pregnant again. The contraceptive methods that can be used during this period include barrier methods (condom and vaginal diaphragm), which can be used without any risk, and hormonal methods, which will vary in type depending on whether the woman is breastfeeding or not. Combined hormonal contraceptives are contraindicated in breastfeeding, but those that are only gestagenic are the ones of choice. IUDs can also be used after childbirth but only when it is approved following certain medical checks.

**Contraception methods and sexuality.** Contraception is recognized today as a right for many couples. One determining factor of a mature sexual relationship is the existence of contraceptive methods that allow the couple to dissociate sexual intercourse from pregnancy. The implied link between sexual intercourse and contraception becomes evident.

The adoption of a contraceptive method can provide reassurance for both men and women entering a sexual relationship who do not want the risk of

unwanted pregnancy. COHC use is better tolerated by men; however, the male condom is well tolerated by women. The methods considered to be of low efficiency, such as natural methods and coitus interruptus, can cause insecurity. However, these options also respond to certain natural or ideological approaches and are the result of choice, and, in many cases, can lead to a better relationship. The combination of more than one type of natural method, in addition to the contributions that new technologies have made to its foundations, can greatly increase the effectiveness of natural methods. It is obvious to think that natural methods, except for some, such as breastfeeding, interfere with the spontaneity of sexual relations, since the existence of voluntary periods of abstinence is conditioned to avoid pregnancy. They also require considerable discipline and motivation, which can significantly influence the sexual activity of the couple.

Other contraceptive methods (hormonal, IUD) allow, at any time and phase of the woman's cycle, for a high degree of confidence in the establishment of sexual relations with a low risk of pregnancy. This can make relationships more spontaneous and eliminate various problems that are often attributed to other contraceptive methods (such as barrier methods). In many cases, the physical changes derived from the use of hormonal contraception, such as the increase in breast volume, the improvement of dysmenorrhea, the reduction of acne, the regularization of the cycle, etc., can be experienced positively, contributing to the improvement of one's own image and sexuality.

# 10. BASIC CONCEPTS IN SEXOLOGY

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**Sex:** a characteristic that can be observed in individuals and in each of their cells, different to sexuality.

**Sexuality:** the set of attributes and behaviors attributed to a certain sex. Sexuality refers to:

- the biological structures related to sex, their anatomo-physiological basis, and their hormonal and neurological regulation
- the cultural structures linked to sexuality and the formation and development of sexual desire
- personal experiences and sexual manifestations.

**Sexual identity:** the feeling of belonging to a certain sex.

**Sexual response:** research on sexual response clearly shows how physiological changes and emotions are closely related. Initially, sexual response was defined as the set of anatomical and physiological reactions that can be observed when an individual responds to an effective sexual stimulus. Nowadays, human sexual response can be defined as the set of anatomical, physiological, and emotional changes that occur as a result of sexual activity and largely involve highly pleasant sensations for the whole organism. Over the years, various models of sexual response have been developed and studied.

**Sexual desire:** sexual desire is a complex concept to define; nonetheless, clarifying this concept allows for a better understanding of female sexual dysfunction. Sexual desire can be understood as an emotion sustained at a biophysiological level (sexual system), consisting of anatomical, physiological, and neuroendocrine elements as well as cognitive components formed by the processing of information since birth. The reference to the sexual system alludes to the need to understand this system in the same way we understand other systems in the human body. The body is a sexual product and producer as well as an essential condition for the manifestation of sexuality. The sexual system may be shaped not only by biological, psychological, and social factors, but also by environmental factors. This new perspective refers to the way in which individuals assign meaning and emotional significance to experiences, which can in turn lead to facilitating or inhibiting sexual responses.

**Sexual activity:** the specific exercise of the sexual function. The practice of the sexual function may be spontaneous (while sleeping), individual (masturbation), homosexual, or heterosexual. Sexual function may also develop physiologically or abnormally. In the case of abnormal sexual function, there exists sexual dysfunction. Appropriate response to sexual stimulus is absent. This differs from cases where there is an appropriate sexual response to an inappropriate object. These are referred to as paraphilias, since the sexual response does not involve two adults:

- fetishism: with a material object
- bestiality or zoophilia: with an animal
- pederasty or pedophilia: with a child.

**Components of an individual's sex.** There are five components that exist harmoniously in most individuals. When there is a contradiction between these components, we speak of intersex. Discrepancies can exist between chromosomal sex and gonadal or genital sex. Transexuals are the reflection of psychological intersex.

- **Chromosomal sex.** This refers to the chromosomal properties of each cell. The normal karyotype (chromosome count) in humans is made up of 46 chromosomes: 44 autosomes and 2 heterochromosomes.

The latter determine sex. They are the first component of sex that we carry in each and every cell.

- **Gonadal sex.** Individuals with testicles are male, and those with ovaries are female.
- **Genital sex or assigned sex.** This is the sex assigned at birth according to the appearance of external genitalia.
- **Psychological sex.** An individual's sexual identity. This is established at around 3 years of age rather than at birth.
- **Sociological sex.** This refers to an individual's social behavior according to their sex and is purely cultural.

**Sexual rights.** In 1975, the WHO defined sexual health as "the integration of the somatic, emotional, intellectual and social aspects of sexual being, in ways that are positively enriching and that enhance personality, communication and love." This was revised in 2000, and sexual health was defined as "a state of physical, emotional, mental and social well-being related to sexuality."

In 1997, the Universal Declaration of Sexual Rights was put forward based on the idea that sexual rights are fundamental and universal human rights based on freedom, dignity, and equality for all human beings. The declaration urged that sexual rights must be recognized, promoted, respected, and defended by all societies through all means, and supported the following:

1. The right to sexual freedom. Sexual freedom encompasses the possibility for individuals to express their full sexual potential. However, this excludes all forms of sexual coercion, exploitation, and abuse at any time and in any situation in life.
2. The right to sexual autonomy, sexual integrity, and safety of the sexual body. This right involves the ability to make autonomous decisions about one's sexual life within a context of one's own personal and social ethics. It also encompasses control and enjoyment of our own bodies, free from torture, mutilation, and violence of any sort.
3. The right to sexual privacy. This involves the right to express sexual preferences in one's private life, as long as they do not intrude on the sexual rights of others.
4. The right to sexual equity. This refers to freedom from all forms of discrimination regardless of sex, gender, sexual orientation, age, race, social class, religion, or disability, whether physical, intellectual, or sensory.
5. The right to sexual pleasure. Sexual pleasure, including autoeroticism, is a source of physical, psychological, intellectual, and spiritual wellbeing.
6. The right to emotional sexual expression. Sexual expression is more than erotic pleasure or sexual acts. Individuals have a right to express their sexuality through communication, touch, emotional expression, and love.
7. The right to freedom of sexual association. This means the possibility to marry or not, to divorce, and to establish other types of sexual associations.
8. The right to make free and responsible reproductive choices. This encompasses the right to decide whether or not to have children, the number and spacing of children, and the right to full access to methods of fertility regulation.
9. The right to sexual information based upon scientific inquiry. This right implies that sexual information should be generated through the process of unencumbered and yet scientifically ethical inquiry and disseminated in appropriate ways at all societal levels.
10. The right to comprehensive sex education. This is a lifelong process from birth throughout the life cycle and should involve all social institutions.
11. The right to sexual healthcare. Sexual healthcare should be available for prevention and treatment of all sexual concerns, problems, and disorders.

**Medical history in sexology.** This is essential to diagnosing and treating sexual problems, since these are rarely referred to or investigated by medical professionals. As a result, many disorders remain undiagnosed and untreated.

The aims of the clinical interview in sexology are:

- to determine the precise nature of the problem
- to evaluate the possible causes
- to establish an initial interaction with therapeutic goals.

However, the following factors may lead to lack of information:

- patient-related factors: fear, embarrassment, ignorance, lack of interest or collaboration, psychological state, medication, or disease-related symptoms
- consultant-related factors: discomfort dealing with subject, lack of information, interpersonal relationship (gender or age difference, etc.), or lack of confidence in the role
- environmental factors: time requirements or presence of others.

**The first appointment:**

- Individuals should always be interviewed individually.
- Confidentiality should be guaranteed.
- The person who sought help should be interviewed first.
- It may be helpful to establish a timeframe.
- Cultural and linguistic problems should be assessed.

The **areas to evaluate** are:

- the nature of the problem
- family and early childhood medical history
- pubertal development
- relationship with partner
- studies/work
- medical/mental health record
- addictions
- complementary tests.

In the interests of systematization, instruments designed to assess both specific and global sexual function have been developed. These include standardized self-administered questionnaires, a daily log, or structured clinical interviews designed to examine female sexual function in a range of clinical settings and the effect different treatments have on the patient. However, many of these instruments are either not validated in Spanish, or they have limited accessibility or usefulness in clinical practice.

Two questionnaires that have been validated are:

- The Brief Profile of Female Sexual Function (B-PFSF)Derogatis, et al., 2004).
- This questionnaire is designed for women who experience decreased sexual desire and are distressed by this decrease. It aims to help them to decide whether they should consult a medical professional. In this questionnaire, users are asked about their feelings around sexuality, sexual activity, and any concerns related to their level of interest in sex over the last 2 to 3 months. Users are instructed to read each sentence carefully and circle the number that best corresponds to their experiences over the last 2 to 3 months. A total score of between 0 and 20 on the B-PFSF indicates that the user may be experiencing low sexual desire that causes distress (also known as hypoactive sexual desire disorder).
- Female Sexual Distress Scale (FSDS) (Derogatis, et al., 2002).

This questionnaire consists of 12 questions that allow women to analyze their own levels of distress in relation to their sex lives in the preceding months.

Both questionnaires display the following characteristics:

- They are designed for women who experience low sexual desire.
- They assess the level of concern and distress.
- They ask about women's feelings in relation to sexuality, sexual activity, and the level of interest in sex in the preceding 2 to 3 months.
- They are self-administered.
- They help women to decide whether to consult a medical professional or not.

The nature of the problem, the woman's relationship with her partner, motivation, psychological or psychiatric disorders, addictions, physical illness, and previous or concurrent treatment should be addressed in sex therapy. Whether the sexual dysfunction is primary (a problem in its own right) or secondary (a symptom of a disease, [e.g. vascular disease]) should be taken into consideration.

# 11. SEXUAL DYSFUNCTIONS: GENERALITIES AND FEMALE SEXUAL DYSFUNCTIONS

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## SEXUAL DYSFUNCTION

Sexual dysfunction is a condition that prevents individuals from experiencing satisfaction during sexual activity. It can affect any phase of the sexual response (desire, arousal, orgasm) and/or produce pain during intercourse. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), sexual dysfunction is not an isolated difficulty in sexual response; to be considered as a sexual dysfunction, the condition has to be present for at least 6 months, have a frequency of 75% to 100% of attempts, and cause significant distress. Another criterion that is also applicable to all diagnoses is that the condition should not be better explained by a "nonsexual mental disorder, a consequence of severe relationship distress (e.g., partner violence) or other significant stressors."

*The DSM-5 diagnoses specify whether the disorder is due to psychological or combined factors, and if it is:*

- lifelong versus acquired
- generalized versus situational
- mild, moderate, or severe
- there is also a group of "associated features," subdivided into five categories:
  - partner factors: partner health status, or partner sexual problems
  - relationship factors, such as lack of communication, discrepancies in sexual activity and/or in desire and/or frequency
  - individual vulnerability factors, such as depression, anxiety, job loss, bereavement, poor body image, history of sexual abuse
  - cultural, religious, or educational factors, when they carry negative attitude toward sexuality, inhibitions, or prohibitions against sexual activity or pleasure
  - medical factors that can be relevant for evolution of the disorder.

## MALE AND FEMALE SEXUAL DYSFUNTIONS

### Substance-induced/medication-induced sexual dysfunction

Appears directly related to the use, modification, intoxication, or abstinence to a substance or medication (it does not occur exclusively during the course of a delirium). The most typical causes are the use of alcohol, opiates, sedatives, hypnotics, anxiolytics, amphetamines, or cocaine. Other substances, coded as unknown, can cause male and female sexual dysfunction.

### Other specified sexual dysfunctions and unspecified sexual dysfunction

Some sexual disorders can produce significant distress but are not described by the sexual dysfunction criteria found in the DSM-5. The disorder can either be specified (e.g., "aversion") or not (unspecified sexual dysfunction).

### Female sexual dysfunctions.

### Female sexual interest/arousal disorder.

The DSM-5 merged female hypoactive desire dysfunction and female arousal dysfunction into a new term: *female sexual interest/arousal disorder* (FSIAD), which was developed following the findings of a large

body of research that suggested the separation between desire and arousal is artificial. The diagnosis requires the presence of three or more of the following symptoms:

1. absence or marked reduction of interest in sexual activity
2. absence or marked reduced of sexual fantasies or erotic thoughts
3. female disinclination to initiate sexual encounters with her partner
4. absence or marked reduction of arousal or sexual pleasure during sexual activity (75% to 100% of attempts, in all contexts)
5. absence or marked reduction of arousal or sexual pleasure as a response to sexual stimulation or invitation
6. female does not feel any sense of pleasure, weather genital or nongenital, during sexual activity.

Individuals frequently suffer secondary low sexual desire as a consequence of nonsatisfactory sexual activity due to physical or psychological ailments as well as a coexisting sexual dysfunction.

**Etiology.** FSIAD is a complex condition affecting women of all ages. The exact cause is not always known because it is often due to multiplicity of factors, each of which are necessary to investigate in order to plan the correct intervention. These include:

*Physical factors:*

1. Low dopamine levels, high serotonin action, reduction of sexual hormones (estrogen and testosterone), high prolactin levels, low thyroxine levels
2. Physical body changes due to:
   a. age: neurovascular mechanisms involved in sexual response
   b. medical conditions and treatments, including diabetes, multiple sclerosis, neurological or vascular problems, mental problems, use of several medicines (antidepressants, antihypertensives), hypothyroidism, genital diseases (chronic irritation, infections, cancer, low tropism, lichen sclerosus), sickness affecting general wellbeing
   c. hormonal changes, including postpartum, menopause (low estrogens level during postmenopause could provide changes in erotic sensations, arousability, orgasm)
3. substance use, including nicotine, cannabis, alcohol, and others

*Psychological factors:*

- personal factors, such as negative attitude toward sexuality due to educational or cultural factors, or personal experiences (sexual trauma, nonsatisfactory previous sexual activity), gender role, poor body image
- relationship issues, such as poor communication, kind and quality of affective relationship, routine, loss of sexual attraction
- external stressors.

**Diagnosis.** It is extremely important to evaluate all these factors through anamnesis, and if it is necessary, to order blood tests to rule out or confirm medical conditions to treat. A physical exam could provide information about hormonal impregnation of tissues and signs of infection. Several questionnaires can be used for initial evaluation, including the Brief Index of Sexual Functioning for Women (BISF-W) and Female Sexual Function Index (FSFI).

**Treatment.** The first step for treatment should be gathering patient information and providing sex education, trying to reduce anxiety and negative ideas about the problem itself and about its influence on self-esteem. It is necessary to modify cognitive and motivational aspects of sexual activity and to discuss the couple's relationship issues, such as communication.

The second step involves acting on identified causal factors, taking into account that new factors can appear during the intervention. Encourage women to modify their lifestyles by focusing on self-care (encourage smokers to stop smoking, promote healthy habits like routine exercise), and adjust medications as needed based on medical recommendations.

The third step focuses on individualized recommendations to improve sexual experience and reconnect with eroticism. To modify sexual activity, reduce the genital part of the sexual experience and increase the connection to general nongenital sensations. Use of lubricants and toys to enhance physical sensations could be evaluated.

Pharmacotherapy for FSIAD is not well developed, mainly because of its multiple causative factors. Flibanserin can be used to increase sexual desire. Although the evidence is not strong and there are different expert opinions about its efficacy, it is the only drug with label indication for low desire in women. It is currently available only in the United States.

There is limited but positive evidence supporting the use of other medications and treatments in FSIAD, including bupropion, tibolone, hormonal treatment for menopause, testosterone, dehydroepiandrosterone, and some phytotherapies, including Ginkgo biloba,

maca, and damiana. Other drugs may increase sexual experience by enhancing quality of life (HTM, phytoestrogens), and there are some of them whose mechanism of action over sexual desire remains unknown. Ospemifene is one drug with on-label indication for dyspareunia. It improves all changes of vaginal and genital atrophy due to lack of estrogens. It has been shown to positively affect sexual desire, but it remains unknown if this effect is because of better sexual experience or because the drug directly increases the desire.

## FEMALE ORGASMIC DISORDER

One of the most frequent female sexual dysfunctions, female orgasmic disorder, occurs if at least one of the two following signs is present:

- absence or marked delayed orgasm in 75% to 100% of attempts, in all contexts, and after an appropriate stimulation, even after feeling sexually arousal
- marked reduction of orgasmic sensations.

Global sexual satisfaction in women is not always correlated with the presence of orgasms. It is one of the sexual dysfunctions in which it is important to determine the related distress to avoid a failed intervention.

Physical causes: they are present in only 5% of women:

1. neurologic problems: spinal cord injury, multiple sclerosis, alcoholic or diabetic neuropathy, amyotrophic lateral sclerosis, spinal tumors
2. endocrinology or metabolic problems: diabetes (evolution in 35% of women), disorders of adrenal or pituitary glands, hyperthyroidism
3. vascular problems: post-myocardial infarction stress, stroke, vasculitis
4. genital problems: dyspareunia, pelvis traumas, gynecological or pelvic surgery, prolapses
5. drugs: methadone, heroin, morphine, codeine, alcohol, tricyclic antidepressants, beta-blockers, barbiturates, codeine
6. personal factors, genetic predisposition, and/or low muscle tone on pelvic floor.

*Psychological causes (more frequent):*

Sexual inexperience, negative feelings about sex or masturbation, woman is unable to relax enough to have an orgasm (anxiety, poor body image, past abuse, feeling fear of losing control), relationship issues. These factors can cause involuntary inhibition of the orgasmic reflex.

**Diagnosis** is directly made by anamnesis. It could be useful to order some test to investigate nonfrequent physical causes. Questionnaires such as the Sexual Arousability Inventory, FSFI, and Golombok-Rust Inventory of Sexual Satisfaction tools can be used to evaluate global conditions.

**Treatment.** Clinicians can facilitate intervention using knowledge of the human sexual response, and by providing patients with sex education and psychological techniques to help anxiety. Clinicians can also guide patients through personal work on negative past experiences and help patients work on self-esteem and partner relationship issues. To modify physical factors, patients should exercise the pelvis floor and introduce lifestyle changes, including relaxation techniques.

While there are no medications to use in this sexual dysfunction, sex therapy often benefits patients. Sex therapy techniques can help women learn new ways to masturbate in a progressive process that begins by improving the knowledge of her anatomy, erogenous zones, and sensations. Sometimes, they have even to learn to build sexual fantasies to help focus attention on the sensations.

Patients can share all knowledge about herself with partner, and they are indicated to start with a nonsexual touching that gradually moves toward sexual intercourses if the couple has an adequate relationship with trust and communication.

### Genito-pelvic pain/penetration disorder

This is a new concept that combines two previous diagnoses: dyspareunia and vaginismus. It is more commonly reported in young women at the beginning of sexual activity and in women around menopause and postmenopausal stage. According to the DSM-5, genito-pelvic pain/penetration disorder appears when one or more of the following symptoms are present:

- persistent difficulty during vaginal penetration
- marked pain in the vulvovaginal or pelvic area during vaginal intercourse or attempts at penetration
- significant fear or anxiety about pain in anticipation of, during, or after vaginal penetration
- tensing or tightening of the pelvic floor muscles when attempting vaginal intercourse.

**Etiology.** All psychological factors providing negative feelings about sexuality, poor knowledge regarding anatomy, sexual response, and relationship issues should be investigated as possible causes (precipitating factors or/and maintenance factors). Psychological

aspects are more common in young women, although it is important to rule out some physical problems by exam (abnormal genital anatomy, fibrous hymen, irritations). Among older women, physical factors are more frequent, with some relationship issues and attitudes toward sexuality as maintaining factors. If women delay consultation, this condition may become worse, leading to the appearance of fear or anxiety. Avoidance of sexual activity and relationship problems may result from this attitude. One of the most important reason for pain during intercourse is the effect of lack of estrogen in the genital tissue. It occurs in postpartum, with some hormonal contraceptives, and, most often, in menopause. It produces low function in mucus, lack of lubrication, vaginal dryness, change in genital sensations, itch, and increase of risk of urinary and vaginal infection. All these symptoms are called genitourinary syndrome of menopause (GSM).

**Diagnosis.** Anamnesis and physical exam should be done in all cases using tests or questionnaires to gauge fear and anxiety and evaluating symptoms of pain. Clinicians should also seek to understand concomitant medications and diseases and should also ask whether previous attempts for a solution were sought and any related outcomes.

**Treatment.** The treatment of the identified cause should always be added to sex counselling. Lubricants improve sexual experience, and help therapy when necessary, but they are not the final solution. GSM can be treated with local estrogens, HT (for menopause), and ospemifeno.

Sex counselling is important to reduce anxiety issues, observation during intercourse, and increase erotic sensations. If anxiety and/or fear are creating tension of pelvic floor muscles, or tightening is evident, sex therapy is necessary. Sex therapy tries to exercise the pelvic floor muscle to improve voluntary control, making this a progressive approach for patients to become comfortable with vaginal penetration by enhancing conscious dilation.